

Docket No: 18-971-0 PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Hidenori OHKI, et al
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HERewith
INTERNATIONAL APPLICATION NO.: PCT/JP95/01983
INTERNATIONAL FILING DATE: September 29, 1995
FOR: NEW COMPOUND

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119
AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

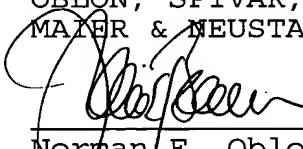
In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

<u>COUNTRY</u>	<u>APPLICATION NO.:</u>	<u>DAY/MONTH/YEAR</u>
JAPAN	9420425.2	07 October 1994
JAPAN	9508745.8	28 April 1995

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. **PCT/JP95/01983**. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,

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MAYER & NEUSTADT, P.C.



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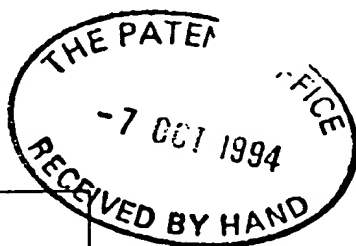
PRIORITY DOCUMENT

Signed

Dated -5 OCT 1995

For official use

9430425.2



12OCT '94H00289710

PAT 1 77 UC

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Your reference

RJG/JLB/2553

Notes

£25

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-437 1700).

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OUT OF
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DATE 07 OCT 1994

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The
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**Request for grant of a
Patent
Form 1/77**

Patents Act 1977

1 Title of invention

1 Please give the title of the invention NEW COMPOUND

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name FUJISAWA PHARMACEUTICAL CO LTD

Country (and State of incorporation, if appropriate) JAPAN

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address 4-7 DOSHOMACHI 3-CHOME
CHUO-KU, OSAKA-SHI
OSAKA 541, JAPAN

UK postcode (if applicable)

Country JAPAN

ADP number (if known)

S9117208001 067

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant (if any)**

2c If you are applying as a corporate body please give:

Corporate name

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③ An address for service in the United Kingdom must be supplied

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③ Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒ No ☐ → go to 3b

↓
please give details below

Agent's name STEVENS, HEWLETT & PERKINS

Agent's address 1 SERJEANTS' INN
FLEET STREET
LONDON

Postcode EC4Y 1LL

Agent's ADP
number 1545003 ✓ JB

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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① Reference number

Agent's or
applicant's reference
number (if applicable)

RJG/JLB/2553

⑤ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Yes ☐ No ☒ ⇒ go to 6

↓
please give details below

☐ number of earlier
application or patent
number

☐ filing date

(day month year)

☐ and the Section of the Patents Act 1977 under which you are claiming:

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

⑥ Declaration of priority

6 If you are declaring priority from previous application(s), please give:

Country of filing

Priority application number
(if known)

Filing date
(day, month, year)

⑥ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

Please mark correct box

Please mark correct box

- 7 The answer must be 'No' if:
- any applicant is not an inventor
 - there is an inventor who is not an applicant, or
 - any applicant is a corporate body.

8 Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

- 9 You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here ➡

A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐

No ☒

A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s)

18

Description

84

Abstract

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 – Statement of Inventorship and Right to Grant (please state how many)

Patents Form 9/77 – Preliminary Examination/Search

Patents Form 10/77 – Request for Substantive Examination

9 Request

I/we request the grant of a patent on the basis of this application.

Stevens, Harold

Signed

Perkins

Date

7

(day)

10

month

94

year

AGENTS FOR THE APPLICANT

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NEW COMPOUND

The present invention relates to new polypeptide compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially, antifungal activities), inhibitory activity on β -1,3-glucan synthase, and further which are expected to be useful for the prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

Accordingly, one object of the present invention is to provide new polypeptide compound and a pharmaceutically

acceptable salt thereof, which are highly active against a number of pathogenic microorganisms and further which are expected to be useful for the prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

Another object of the present invention is to provide a process for the preparation of new polypeptide compound and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said new polypeptide compound or a pharmaceutically acceptable salt thereof.

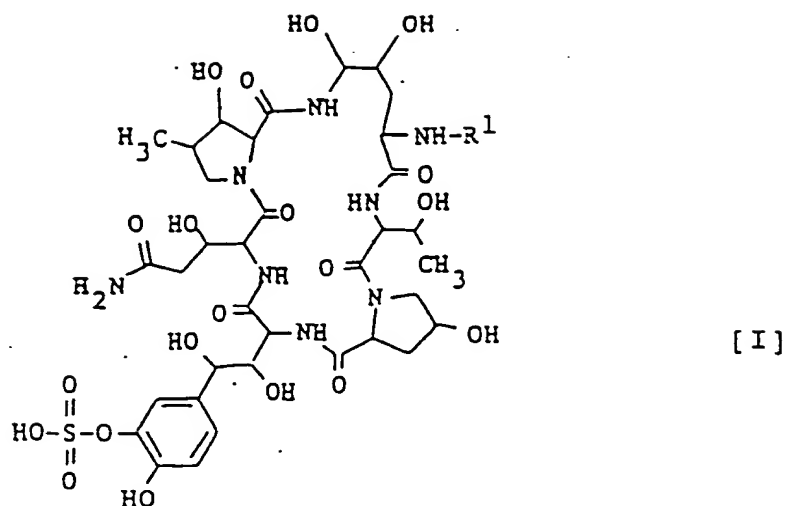
Still further object of the present invention is to provide a method for the prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) caused by pathogenic microorganisms, which comprises administering said new polypeptide compound or a pharmaceutically acceptable salt thereof to a human being or an animal.

An additional object of the present invention is to provide a use of said new polypeptide compound and a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal.

A still additional object of the present invention is to provide a use of said new polypeptide compound and a pharmaceutically acceptable salt thereof for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal.

The object polypeptide compound used in the present invention are new and can be represented by the following

general formula [I] :



wherein R¹ is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable

substituent(s);

lower alkanoyl substituted with saturated
3 to 8 membered heteromonocyclic group
containing at least one nitrogen atom which
may have one or more suitable

substituent(s);

ar(lower)alkenoyl substituted with aryl
which may have one or more suitable
substituent(s);

naphthyl(lower)alkenoyl which may have one
or more higher alkoxy;

lower alkynoyl which may have one or more
suitable substituent(s);

(C₂-C₆)alkanoyl substituted with naphthyl
having higher alkoxy;

ar(C₂-C₆)alkanoyl substituted with aryl
having one or more suitable substituent(s);

aroyl substituted with heterocyclic group
which may have one or more suitable
substituent(s);

aroyl substituted with aryl having
heterocyclic(higher)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower
alkyl;

aroyl substituted with aryl having higher
alkyl;

aryloxy(lower)alkanoyl which may have one
or more suitable substituent(s);

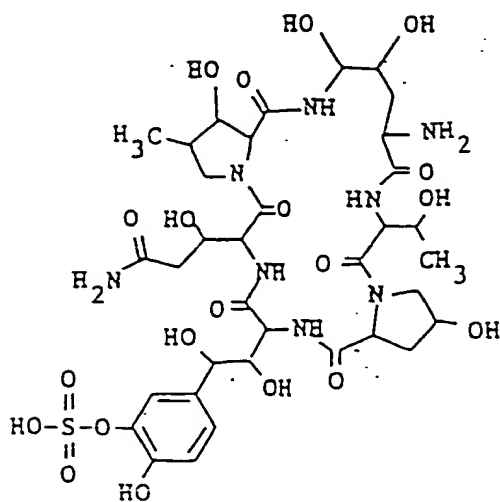
ar(lower)alkoxy(lower)alkanoyl which may
have one or more suitable substituent(s); or

arylamino(lower)alkanoyl which may have
one or more suitable substituent(s).

The new polypeptide compound [I] and a

pharmaceutically acceptable salt thereof can be prepared by the process as illustrated in the following reaction scheme.

Process 1

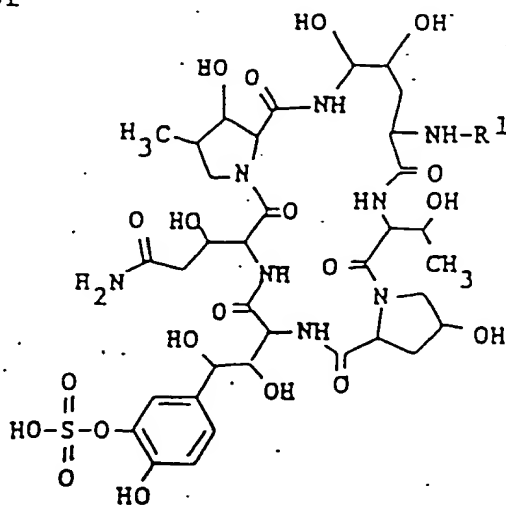


[II]

or its reactive derivative
at the amino group
or a salt thereof

R¹-OH [III]

or its reactive derivative
at the carboxy group
or a salt thereof



[I]

or a salt thereof

wherein R1 is as defined above.

Suitable pharmaceutically acceptable salts of the object polypeptide compound [I] are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 3.

Suitable example of "lower alkanoyl" may include

straight or branched one such as formyl, acetyl, 2-methylacetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl, pentanoyl, 2,2-dimethylpropionyl, hexanoyl, and the like.

5 Suitable example of "suitable substituent(s)" in the groups such as "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more
10 suitable substituent(s)", "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)", etc. may include lower alkoxy as mentioned below, higher alkoxy as mentioned below, lower alkyl as mentioned below, higher alkyl as mentioned below, higher alkoxy(lower)alkyl, lower alkoxycarbonyl, oxo, aryl
15 which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl which may have one or more lower alkyl, aryl which may have one or more higher alkyl, aryl substituted with aryl which may have one or more lower alkoxy, aryl substituted with aryl which may
20 have one or more higher alkoxy, aryl substituted with aryl which may have one or more lower alkyl, aryl substituted with aryl which may have one or more higher alkyl, aroyl which may have one or more lower alkoxy, aroyl which may have one or more higher alkoxy, aroyl which may have one
25 or more lower alkyl, aroyl which may have one or more higher alkyl, heterocyclic group which may have one or more lower alkoxy, heterocyclic group which may have one or more higher alkoxy, aryl having heterocyclic(higher)alkoxy, and the like.

30 Suitable example of "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, and the like,
35 in which the preferred one may be (C₃-C₆)alkoxy, and more preferred one may be butoxy, pentyloxy, and hexyloxy.

Suitable example of "higher alkoxy" may include straight or branched one such as heptyloxy, octyloxy, 3,5-dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, 5 tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like, in which the preferred one may be (C₇-C₁₄)alkoxy, and the more preferred one may be heptyloxy and octyloxy.

Suitable example of "lower alkyl" may include 10 straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, and the like,

15 in which the preferred one may be methyl, pentyl and hexyl.

Suitable example of "higher alkyl" may include straight or branched one having 7 to 20 carbon atoms, such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, 20 pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like,

in which the preferred one may be (C₇-C₁₄)alkyl, and the more preferred one may be heptyl, octyl and nonyl.

Suitable example of "aryl" and "ar" moiety may 25 include phenyl which may have lower alkyl (e.g., phenyl, mesityl, tolyl, etc.), naphthyl, anthryl, and the like, in which the preferred one may be phenyl and naphthyl.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like,

30 in which the preferred one may be benzoyl and naphthoyl.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen 35 atom which may have one or more suitable substituent(s)"

can be referred to aforementioned "lower alkanoyl",
in which the preferred one may be (C₁-C₄)alkanoyl, and
the more preferred one may be formyl.

Suitable example of "unsaturated 6-membered
5 heteromonocyclic group containing at least one nitrogen
atom" in the term of "lower alkanoyl substituted with
unsaturated 6-membered heteromonocyclic group containing
at least one nitrogen atom which may have one or more
suitable substituent(s)" may include pyridyl,
10 dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl,
triazinyl (e.g., 4H-1,2,4-triazinyl, 1H-1,2,3-triazinyl,
etc.), tetrazinyl (e.g., 1,2,4,5-tetrazinyl, 1,2,3,4-
tetrazinyl, etc.), and the like,

in which the preferred one may be unsaturated 6-membered
15 heteromonocyclic group containing 1 to 3 nitrogen atom(s),
and the most preferred one may be pyridyl.

Suitable example of "suitable substituent(s)" in the
term of "lower alkanoyl substituted with unsaturated
6-membered heteromonocyclic groups containing at least one
20 nitrogen atom which may have one or more suitable
substituent(s)" can be referred to aforementioned
"suitable substituent(s)",

in which the preferred one may be higher alkoxy and
higher alkoxy(lower)alkyl, and the more preferred one may
25 be (C₇-C₁₄)alkoxy and (C₇-C₁₄)-
alkoxy(C₁-C₄)alkyl, and the most preferred one may be
octyloxy and octyloxymethyl.

Suitable example of "lower alkanoyl" in the term of
"lower alkanoyl substituted with 1,2,3,4-tetra-
30 hydroisoquinoline which may have one or more suitable
substituent(s)" can be referred to aforementioned "lower
alkanoyl",

in which the preferred one may be (C₁-C₄)-
alkanoyl, and the more preferred one may be formyl.

35 Suitable example of "suitable substituent(s)" in the

term of "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

5 in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl and lower alkoxycarbonyl, and the more preferred one may be (C₇-C₁₄)alkoxy and (C₁-C₄)alkoxycarbonyl, and the most preferred one may be octyloxy and tert-butoxycarbonyl.

10 Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

15 in which the preferred one may be (C₁-C₄)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing at least one oxygen atom" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" may include unsaturated condensed heterocyclic group containing one or more oxygen atom(s) and, optionally, another hetero atom(s) except oxygen atom,

25 in which the preferred one may be unsaturated condensed heterocyclic group containing 1 to 3 oxygen atom(s), unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 2 sulfur atom(s) and unsaturated condensed heterocyclic group 1 to 3 oxygen atom(s) and 1 to 3 nitrogen atom(s), and the more preferred one may be benzo[b]furanyl, isobenzofuranyl, chromenyl, xanthenyl, benzoxazolyl, benzoxadiazolyl, dihydrooxathiinyl, phenoxathiinyl, and the like, and the most preferred one
35 may be benzo[b]furanyl, chromenyl and benzoxazolyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl and oxo, and the more preferred one may be (C₇-C₁₄)alkoxy, (C₁-C₄)alkyl, (C₇-C₁₄)alkyl and oxo, and the most preferred one may be octyloxy, methyl, nonyl, and oxo.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C₁-C₄)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" may include unsaturated condensed heterocyclic group containing only 1 to 3 sulfur atom(s), in which the preferred one may be benzothienyl and benzodithiiny, and the most preferred one may be benzothienyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher

alkoxy, lower alkyl and higher alkyl, and more preferred one may be (C₇-C₁₄)alkoxy, and the most preferred one may be octyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C₁-C₄)alkanoyl, and the most preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" may include 1H-indazolyl, purinyl, phthalazinyl, benzoimidazolyl, naphthyridinyl, quinoxalinyl, quinazolyl, cinnolinyl, pteridinyl, and the like,

in which the most preferred one may be benzoimidazolyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, aryl which may have one or more lower alkoxy and aryl which may have one or more higher alkoxy, and the more preferred one may be (C₇-C₁₄)alkyl and phenyl which may have 1 to 3 (C₁-C₆)alkoxy, and the most preferred one may be nonyl and phenyl which may have 1 to 3 hexyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered

heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C₁-C₄)alkanoyl, and the more preferred one may be formyl.

Suitable example of "saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, and the like,

in which the preferred one may be piperidyl and piperazinyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include lower alkoxy, higher alkoxy, higher alkoxy(lower)alkyl, lower alkyl, higher alkyl, oxo, aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl which may have one or more lower alkyl, aryl which may have one or more higher alkyl, aroyl which may have one or more lower alkoxy, aroyl which may have one or more higher alkoxy, aroyl which may have one or more lower alkyl, aroyl which may have one or more higher alkyl, and the like,

in which the preferred one may be aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aroyl which may have one or more lower alkoxy and aroyl which may have one or more higher alkoxy, and the

more preferred one may be aryl which may have 1 to 3 higher alkoxy and aroyl which may have 1 to 3 higher alkoxy, and the much more preferred one may be phenyl which may have 1 to 3 (C₇-C₁₄)alkoxy and naphthoyl which may have 1 to 3 (C₇-C₁₄)alkoxy, and the most preferred one may be phenyl which may have 1 to 3 octyloxy and naphthoyl which may have 1 to 3 heptyloxy.

Suitable example of "ar(lower)alkenoyl" in the term of "ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s)" may include phenyl(lower)alkenoyl (e.g., 3-phenylacryloyl, (2- or 3- or 4-)phenyl-(2- or 3-)butenoyl, 3-phenylmethacryloyl, (2- or 3- or 4- or 5-)phenyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)phenyl-(2- or 3- or 4- or 5-)-hexanoyl, etc.), naphthyl(lower)alkenoyl (e.g., 3-naphthylacryloyl, (2- or 3- or 4-)naphthyl-(2- or 3-)butenoyl, (2- or 3- or 4- or 5-)naphthyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)naphthyl-(2- or 3- or 4- or 5-)hexanoyl, etc.), and the like, in which the preferred one may be 3-phenylacryloyl.

Suitable example of "suitable substituent(s)" in the term of "ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred "aryl which may have one or more suitable substituent(s)" may be aryl which may have one or more lower alkoxy, aryl which may have one or more lower alkyl and aryl which may have one or more higher alkyl, and the much more preferred one may be phenyl which may have 1 to 3 (C₁-C₆)alkoxy, phenyl which may have 1 to 3 (C₁-C₆)alkyl and phenyl which may have 1 to 3 (C₇-C₁₄)alkyl, and the most preferred one may be phenyl which may have 1 to 3 pentyloxy, phenyl which may have 1 to 3 heptyl and phenyl which may have 1 to 3 pentyl.

Suitable example of "naphthyl(lower)alkenoyl" in the

term of "naphthyl(lower)alkenoyl which may have one or more higher alkoxy" may include 3-naphthylacryloyl, (2- or 3- or 4-)naphthyl-(2- or 3-)butenoyl, (2- or 3- or 4- or 5-)naphthyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)naphthyl-(2- or 3- or 4- or 5-)hexanoyl, and the like,

in which the preferred one may be 3-naphthylacryloyl.

Suitable example of "lower alkynoyl" in the term of "lower alkynoyl which may have one or more suitable substituent(s)" may include 2-propynoyl, (2- or 3-)butynoyl, (2- or 3- or 4-)pentynoyl, (2- or 3- or 4- or 5-)hexynoyl, and the like,

in which the preferred one may be 2-propynoyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkynoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl substituted with aryl which may have one or more lower alkyl and aryl substituted with aryl which may have one or more higher alkyl, and the more preferred one may be aryl substituted with aryl which may have 1 to 3 lower alkyl and aryl which may have 1 to 3 higher alkoxy, and the much more preferred one may be phenyl substituted with phenyl which may have 1 to 3 (C₁-C₆)alkyl and phenyl which may have 1 to 3 (C₇-C₁₄)alkoxy, and the most preferred one may be phenyl substituted with phenyl which may have 1 to 3 pentyl and naphthyl which may have 1 to 3 heptyloxy.

Suitable example of "ar(C₂-C₆)alkanoyl" in the term of "ar(C₂-C₆)alkanoyl substituted with aryl having one or more suitable substituent(s)" may include phenyl(C₂-C₆)alkanoyl {e.g., phenylacetyl, (2- or 3- phenylpropanoyl, 2- or 3- or 4-phenylbutanoyl, 2- or 3- or

4- or 5-)phenylpentanoyl, (2- or 3- or 4- or 5- or 6-phenylhexanoyl, etc.), naphthyl(C₂-C₆)alkanoyl {e.g. naphthylacetyl, (2- or 3-)naphthylpropanoyl, (2- or 3- or 4-)naphthylbutanoyl, (2- or 3- or 4- or 5-
5 naphthylpentanoyl, (2- or 3- or 4- or 5- or 6-naphthylhexanoyl, etc.)}, and the like,

in which the preferred one may be 3-phenylpropanoyl.

Suitable example of "suitable substituent(s)" in the term of "ar(C₂-C₆)alkanoyl substituted with aryl having
10 one or more suitable substituent(s)" may include lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, oxo, aryl having one or more lower alkoxy, aryl having one or more higher alkoxy, aryl having one or more lower alkyl, aryl having one or more higher
15 alkyl, aryl substituted with aryl having one or more lower alkoxy, aryl substituted with aryl having one or more higher alkoxy, aryl substituted with aryl having one or more lower alkyl, aryl substituted with aryl having one or more higher alkyl, and the like,

20 in which the preferred one may be aryl having 1 to 3 lower alkoxy, aryl having 1 to 3 higher alkoxy, aryl having 1 to 3 lower alkyl and aryl having 1 to 3 higher alkyl, and the much more preferred one may be phenyl having 1 to 3 (C₁-C₆)alkoxy and phenyl having 1 to 3 (C₁-C₆)alkyl and the most preferred one may be phenyl having 1
25 to 3 pentyloxy and phenyl having 1 to 3 pentyl.

Suitable example of "(C₂-C₆)alkanoyl" in the term of "(C₂-C₆)alkanoyl substituted with naphthyl having higher alkoxy" may include acetyl, propanoyl, butanoyl,
30 pentanoyl, hexanoyl, and the like,

in which the preferred one may be propanoyl.

Suitable example of "aroyl" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)" may include benzoyl,
35 toluoyl, naphthoyl, and the like,

in which the preferred one may be benzoyl.

Suitable example of "heterocyclic group" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)" may include
5 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-
10 triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4
15 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyll, benzimidazolyl, quinolyl,
20 isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g.,
25 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example,
30 morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur
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atom(s) and 1 to 3 nitrogen atom(s), for example,
thiazolyl, isothiazolyl, thiadiazolyl (e.g.,
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.),
5 dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-
membered) heteromonocyclic group containing 1 to 2 sulfur
atom(s) and 1 to 3 nitrogen atom(s), for example,
thiazolidinyl, etc.;

10 unsaturated 3 to 8-membered (more preferably 5 or 6-
membered) heteromonocyclic group containing 1 to 2 sulfur
atom(s), for example, thienyl, dihydrodithiinyl,
dihydrodithionyl, etc.;

15 unsaturated condensed heterocyclic group containing 1
to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for
example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-
membered) heteromonocyclic group containing an oxygen
atom, for example, furyl, etc.;

20 unsaturated 3 to 8-membered (more preferably 5 or 6-
membered) heteromonocyclic group containing an oxygen atom
and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl,
etc.;

25 unsaturated condensed heterocyclic group containing 1
to 2 sulfur atom(s), for example, benzothienyl,
benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing
an oxygen atom and 1 to 2 sulfur atom(s), for example,
benzoxathiinyl, etc.; and the like,

30 in which the preferred one may be saturated 3 or 8-
membered heteromonocyclic group containing 1 to 4 nitrogen
atom(s), and the most preferred one may be piperazinyl.

35 Suitable example of "suitable substituent(s)" in the
term of "aroyl substituted with heterocyclic group which

may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be aryl which may have 1 to 3 higher alkoxy, and the more preferred one may be phenyl which may have 1 to 3 (C₇-C₁₄)alkoxy, and the most preferred one may be phenyl which may have 1 to 3 octyloxy.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,

in which the preferred one may be benzoyl.

Suitable example of "heterocyclic" moiety in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy" can be referred to the ones as exemplified before for "heterocyclic group" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)",

in which the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and the most preferred one may be triazolyl.

Suitable example of "(higher)alkoxy" in the term of "aroyl substituted with aryl having heterocyclic(higher)-alkoxy" can be referred to aforementioned higher alkoxy,

in which the preferred one may be (C₇-C₁₄)alkoxy, and the most preferred one may be octyloxy.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy" can be referred to aforementioned "aryl",

in which the preferred one may be phenyl.

Suitable example of "aroyl substituted with 2 lower alkoxy" may include benzoyl substituted with 2 lower alkoxy and naphthoyl substituted with 2 lower alkoxy,

in which the preferred one may be benzoyl substituted with 2 (C₁-C₆)alkoxy, and the most preferred one may be

benzoyl substituted with 2 pentyloxy.

Suitable example of "aroyl substituted with aryl having lower alkyl" may include benzoyl substituted with phenyl having lower alkyl, benzoyl substituted with naphthyl having lower alkyl, naphthoyl substituted with phenyl having lower alkyl, naphthoyl substituted with naphthyl having lower alkyl, and the like,

in which the preferred one may be benzoyl substituted with phenyl having (C₁-C₆)alkyl, and the most preferred one may be benzoyl substituted with phenyl having hexyl.

Suitable example of "aroyl substituted with aryl having higher alkyl" may include benzoyl substituted with phenyl having higher alkyl, benzoyl substituted with naphthyl having higher alkyl, naphthoyl substituted with phenyl having higher alkyl, naphthoyl substituted with naphthyl having higher alkyl, and the like,

in which the preferred one may be benzoyl substituted with phenyl having (C₇-C₁₄)alkyl, and the most preferred one may be benzoyl substituted with phenyl having heptyl.

Suitable example of "aryloxy" moiety in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenoxy, mesityloxy, tolyloxy, naphthyloxy, anthryloxy, and the like,

in which the preferred one may be phenoxy.

Suitable example of "lower alkanoyl" moiety in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be formyl, acetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl and pentanoyl, hexanoyl, and the more preferred one may be (C₁-C₆)alkanoyl, and the much more preferred one may be formyl, acetyl, propionyl and 2,2-dimethylacetyl.

Suitable example of "suitable substituent(s)" in the term of "aryloxy(lower)alkanoyl which may have one or more

suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be (C₇-C₁₄)alkoxy, and the more preferred one may be octyloxy.

5 Suitable example of "ar(lower)alkoxy" moiety in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" may include

10 phenyl(lower)alkoxy {e.g., phenylmethoxy, (1- or 2-phenylethoxy, phenylpropoxy, 2-phenyl-1-methylpropoxy, 3-phenyl-2,2-dimethylpropoxy,

(1- or 2- or 3- or 4-)phenylbutoxy, (1- or 2- or 3- or 4- or 5-)phenylpentyloxy, (1- or 2- or 3- or 4- or 5- or 6-phenylhexyloxy, etc.}, naphthyl(lower)alkoxy {e.g.

15 naphthylmethoxy, (1- or 2-)naphthylethoxy, 1-naphthylpropoxy, 2-naphthyl-1-methylpropoxy, 3-naphthyl-2,2-dimethylpropoxy, (1- or 2- or 3- or 4-)naphthylbutoxy, (1- or 2- or 3- or 4- or 5-)naphthylpentyloxy, (1- or 2- or 3- or 4- or 5- or 6-)naphthylhexyloxy, etc.}, and the like,

20 in which the preferred one may be naphthyl(C₁-C₄)alkoxy, and the more preferred one may be naphthylmethoxy.

25 Suitable example of "(lower)alkanoyl" moiety in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C₁-C₄)alkanoyl, and the more preferred one may be formyl.

30 Suitable example of "suitable substituent(s)" in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

35 in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl and higher alkyl, and the more preferred one may be higher alkoxy, and the much more preferred one may be (C₇-C₁₄)alkoxy, and the most

preferred one may be heptyloxy.

Suitable example of "arylamino" moiety in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenylamino, mesitylamino, tolylamino, naphthylamino, anthrylamino and the like,

in which the preferred one may be phenylamino and naphthylamino.

Suitable example of "lower alkanoyl" in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C₁-C₄)alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, aryl which may have 1 to 3 lower alkoxy and aryl which may have 1 to 3 higher alkoxy, and the more preferred one may be (C₇-C₁₄)alkoxy, and phenyl which may have 1 to 3 (C₇-C₁₄)alkoxy, and the most preferred one may be heptyloxy and phenyl which may have 1 to 3 heptyloxy.

The process for preparing the object polypeptide compound [I] or a salt thereof of the present invention are explained in detail in the following.

Process 1

The object polypeptide compound [I] or a salt thereof can be prepared by reacting the compound [II] or its reactive derivative at the amino group or a salt thereof with the compound [III] or its reactive derivative at the

carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the mind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the object polypeptide compound [I].

5 The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence
10 the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [III] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional
15 condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide,
20 N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-2-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus
25 oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt;
30 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with
35 thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorous oxychloride, methanesulfonyl chloride, etc.;

or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The starting compound [II] is a known compound. It can be prepared by fermentation and synthetic processes disclosed in EP 0462531 A2.

A culture of *Coleophoma* sp. F-11899, which is used in said fermentation process, has been deposited with National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology (former name: Fermentation Research Institute Agency of Industrial Science and Technology) (1-3, Higashi 1-chome, Tsukubashi, IBARAKI 305, JAPAN) on October 26, 1989 under the number of FERM BP-2635.

The compounds obtained by the above Process 1 can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, high-performance liquid chromatography (HPLC), reprecipitation, or the like.

The compounds obtained by the above Process 1 may be obtained as its hydrate, and its hydrate is included within the scope of this invention.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric

carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

Biological property of the polypeptide
compound [I] of the present invention

In order to show the usefulness of the polypeptide compound [I] of the present invention, the biological data of the representative compound is explained in the following.

Test 1 (Antimicrobial activity) :

In vitro antimicrobial activity of the compound of Example 17 disclosed later was determined by the two-fold agar-plate dilution method as described below.

Test Method

One loopful of an overnight culture of each test microorganism in Sabouraud broth containing 2% Glucose (10^5 viable cells per ml) was streaked on yeast nitrogen base dextrose agar (YNBDA) containing graded concentrations of the object polypeptide compound [I], and the minimal inhibitory concentration (MIC) was expressed in terms of $\mu\text{g/ml}$ after incubation at 30°C for 24 hours.

Test Result

MIC ($\mu\text{g/ml}$)

Test Compound Test organism	The compound of <u>Example 17</u>
candida albicans FP-633	0.2

From the test result, it is realized that the object polypeptide compound [I] of the present invention has an antimicrobial activity (especially, antifungal activity).

5 The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the object polypeptide compound (I) or a pharmaceutically acceptable salt thereof, as an
10 active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular)
15 administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

 The active ingredient may be compounded, for example,
20 with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams, ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or
25 suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly
30 may be used as additives.

 The object polypeptide compound [I] or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired antimicrobial effect upon the
35 process or condition of diseases.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, or insufflation. While the dosage of therapeutically effective amount of the object polypeptide compound [I] varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-20 mg of the object polypeptide compound [I] per kg weight of human being in the case of intramuscular administration, a daily dose of 0.1-20 mg of the object polypeptide compound [I] per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the object polypeptide compound [I] per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment of prevention of Pneumocystis carinii infection, the followings are to be noted.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

Alternatively, parenteral administration may be employed using drip intravenous administration.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

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Preparation 1

To a suspension of 1-(4-hydroxyphenyl)-4-tert-butoxycarbonylpiperazine (3 g) and potassium carbonate (0.82 g) in N,N-dimethylformamide (15 ml) was added octyl bromide (1.87 ml). The mixture was stirred for 10 hours at 70°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel, and eluted with (hexane : ethyl acetate = 9:1). The fractions containing the object compound were combined, and evaporated under reduced pressure to give 1-(4-n-octyloxyphenyl)-4-tert-butoxycarbonylpiperazine (2.71 g).

IR (KBr) : 1687, 1513, 1241 cm^{-1}

NMR (CDCl_3 , δ) : 0.88 (3H, t, $J=6.2\text{Hz}$), 1.2-1.4 (10H, m), 1.48 (9H, s), 1.65-1.85 (2H, m), 3.00 (4H, t, $J=5.2\text{Hz}$), 3.57 (4H, t, $J=5.2\text{Hz}$), 3.90 (2H, t, $J=6.5\text{Hz}$), 6.83 (2H, dd, $J=6.4$ and 2.1Hz), 6.89 (2H, dd, $J=6.4$ and 2.1Hz)

Preparation 2

A solution of 1-(4-n-octyloxyphenyl)-4-tert-butoxycarbonylpiperazine (2.61 g) in trifluoroacetic acid (20 ml) was stirred for 4 hours at ambient temperature. The reaction mixture was evaporated under reduced pressure, and to the residue was added a mixture of 1N NaOH aqueous solution and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-(4-n-octyloxyphenyl)piperazine (0.86 g).

IR (KBr) : 2923, 1513, 1259, 831 cm^{-1}

NMR (CDCl_3 , δ) : 0.88 (3H, t, $J=6.4\text{Hz}$), 1.2-1.53

(10H, m), 1.65-1.85 (2H, m), 3.03 (4H, s), 3.90
(2H, t, J=6.5Hz), 6.83 (2H, dd, J=6.4 and
2.9Hz), 6.90 (2H, dd, J=6.4 and 2.9Hz)
APCI-MASS : e/z = 291 ($M^+ + 1$)

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Preparation 3

To a suspension of 1-(4-n-octyloxyphenyl)piperazine
(1 g) and potassium carbonate (0.476 g) in N,N-dimethyl-
formamide (1 ml) was added p-fluorobenzonitrile (0.347 g),
10 and stirred for 5 hours at 160°C. The reaction mixture
was added to a mixture of water and ethyl acetate. The
organic layer was taken, and dried over magnesium sulfate.
The magnesium sulfate was filtered off, and the filtrate
was evaporated under reduced pressure to give 4-[4-(4-n-
15 octyloxyphenyl)piperazin-1-yl]benzonitrile (0.93 g).

IR (KBr) : 2848, 2217, 1604, 1511, 1241 cm^{-1}

NMR (CDCl_3 , δ) : 0.89 (3H, t, J=6.8Hz), 1.2-1.53

(10H, m), 1.65-1.85 (2H, m), 3.20 (4H, t,

J=5.4Hz), 3.48 (4H, t, J=5.4Hz), 3.91 (2H, t,

20 J=6.5Hz), 6.8-7.0 (6H, m), 7.52 (2H, d, J=8.9Hz)

APCI-MASS : e/z = 392 ($M^+ + 1$)

Preparation 4

A mixture of 2,4-dihydroxybenzaldehyde (5.52 g),
25 potassium carbonate (6.08 g) and octyl bromide (7.73 g) in
acetonitrile (55 ml) was stirred for 16 hours at 60°C.
The solvent of reaction mixture was removed under reduced
pressure, and the residue was dissolved in ethyl acetate,
and washed with water and brine. The separated organic
30 layer was dried over magnesium sulfate. The magnesium
sulfate was filtered off, and the filtrate was evaporated
under reduced pressure. The residue was subjected to
column chromatography on silica gel and eluted with
(hexane : ethyl acetate = 9:1) to give 2-hydroxy-4-
35 octyloxybenzaldehyde (6.73 g).

NMR (CDCl_3 , δ) : 0.89 (3H, t, $J=8.8\text{Hz}$), 1.2-1.5
(10H, m), 1.8-2.0 (2H, m), 4.0-4.2 (2H, m), 6.42
(1H, s), 6.52 (1H, d, $J=8.7\text{Hz}$), 7.79 (1H, d,
 $J=8.7\text{Hz}$), 10.33 (1H, s)

APCI-MASS : $e/z = 257$ (M^++1)

Preparation 5

The following compound was obtained according to a
similar manner to that of Preparation 4.

Methyl 3,4-dipentyloxybenzoate

NMR (CDCl_3 , δ) : 0.93 (6H, t, $J=6.0$ and 9.0Hz), 1.3-
2.0 (12H, m), 3.88 (3H, s), 4.04 (4H, m),
6.86 (1H, d, $J=8.4\text{Hz}$), 7.53 (1H, d, $J=2.0\text{Hz}$),
7.63 (1H, dd, $J=8.4$ and 2.0Hz)

APCI-MASS : $e/z = 309$ (M^++1)

Preparation 6

A mixture of 4-bromo-4'-pentylbiphenyl (5.04 g),
trimethylsilylacetylene (2.4 ml),
tetrakis(triphenylphosphine)palladium (0.96 g),
triphenylphosphine (0.22 g) and cuprous iodide (95 mg) in
piperidine (10 ml) was heated for an hour under
atmospheric pressure of nitrogen at 90°C . The reaction
mixture was poured into a mixture of cold water and ethyl
acetate, and adjusted to about pH 1 with 6N hydrochloric
acid. The separated organic layer was washed with water
and brine, and dried over magnesium sulfate. The
magnesium sulfate was filtered off, and the filtrate was
evaporated under reduced pressure to give crude 2-[4-(4-
pentylphenyl)phenyl]-1-trimethylsilylacetylene, which was
used for the next reaction without further purification.
Crude mixture was dissolved in a mixture of
dichloromethane (10 ml) and methanol (10 ml), and to the
solution was added potassium carbonate (2.75 g) at 0°C .

The mixture was allowed to warm to ambient temperature, and stirred for another 2 hours. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and the resultant precipitate was filtered off. The filtrate was adjusted to about pH 7 with 1N hydrochloric acid, and washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude powder, which was subjected to column chromatography on silica gel (300 ml), and eluted with a mixture of (n-hexane : ethyl acetate = 99:1 - 97:3, V/V) to give 4-(4-pentylphenyl)phenylacetylene (2.09g).

IR (Nujol) : 3274, 1490 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=6.4\text{Hz}$), 1.30-1.50 (4H, m), 1.50-1.80 (2H, m), 2.64 (2H, t, $J=7.6\text{Hz}$), 7.20-7.30 (2H, m), 7.45-7.60 (6H, m)

APCI-MASS : $e/z = 281$ ($M^+ + 1$ + MeOH)

Preparation 7

The following compound was obtained according to a similar manner to that of Preparation 6.

6-heptyloxynaphthalen-2-yl-acetylene

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=6.5\text{Hz}$), 1.20-1.60 (8H, m), 1.70-1.90 (2H, m), 3.10 (1H, s), 4.07 (2H, t, $J=6.5\text{Hz}$), 7.08 (1H, d, $J=2.5\text{Hz}$), 7.15 (1H, dd, $J=2.5$ and 8.9Hz), 7.47 (1H, dd, $J=1.6$ and 8.5Hz), 7.64 (1H, d, $J=7.3\text{Hz}$), 7.68 (1H, d, $J=8.5\text{Hz}$), 7.94 (1H, d, $J=1.6\text{Hz}$)

APCI-MASS : $e/z = 267$ ($M^+ + 1$)

Preparation 8

To a solution of 4-(4-pentylphenyl)phenylacetylene (2.09 g) in tetrahydrofuran (30 ml) was added dropwise a solution of lithium diisobutylamide in a mixture of

tetrahydrofuran and n-hexane (1.60 M, 5.6 ml) at -75°C, and the resultant mixture was stirred for an hour at -78°C. To the mixture was added methyl chloroformate (0.72 ml), and the reaction mixture was allowed to warm to ambient temperature. The solution was diluted with ethyl acetate, and washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude product, which was subjected to column chromatography on silica gel (150 ml), and eluted with a mixture of (n-hexane : ethyl acetate = 100:0 - 9:1, V/V) to give methyl 3-[4-(4-pentylphenyl)phenyl]propionate (2.20 g).

IR (Nujol) : 2225, 1712 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=6.5\text{Hz}$), 1.25-1.50 (4H, m), 1.52-1.80 (2H, m), 2.64 (2H, t, $J=7.6\text{Hz}$), 3.85 (3H, s), 7.20-7.35 (2H, m), 7.40-7.70 (6H, m)

APCI-MASS : $e/z = 307 (M^++1)$

Preparation 9

The following compound was obtained according to a similar manner to that of Preparation 8.

Methyl 3-(6-heptyloxynaphthalen-2-yl)propionate

IR (Nujol) : 2219, 1704, 1621 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=6.5\text{Hz}$), 1.20-1.60 (8H, m), 1.70-2.00 (2H, m), 3.86 (3H, s), 4.08 (2H, t, $J=6.5\text{Hz}$), 7.10 (1H, d, $J=2.5\text{Hz}$), 7.17 (1H, dd, $J=2.5$ and 8.9Hz), 7.52 (1H, dd, $J=1.6$ and 8.5Hz), 7.68 (1H, d, $J=7.3\text{Hz}$), 7.72 (1H, d, $J=8.5\text{Hz}$), 8.06 (1H, d, $J=1.6\text{Hz}$)

APCI-MASS : $e/z = 325 (M^++1)$

Preparation 10

A mixture of 4-bromo-4'-pentylbiphenyl (5.0 g), methyl acrylate (2.2 ml), palladium acetate (0.11 g) and tris(o-tolyl)phosphine (0.60 g) in triethylamine (16 ml) was refluxed for 15 hours under nitrogen atmosphere. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 1.5 with 6N hydrochloric acid. The separated organic layer was washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude powder, which was subjected to column chromatography on silica gel (200 ml), and eluted with a mixture of (n-hexane : ethyl acetate = 100:0 - 94:6, V/V) to give methyl 3-[4-(4-pentylphenyl)phenyl]-acrylate (4.48 g).

IR (Nujol) : 1718, 1637 cm^{-1}

NMR (CDCl_3 , δ) : 0.91 (3H, t, $J=6.7\text{Hz}$), 1.20-1.50 (4H, m), 1.50-1.80 (2H, m), 2.65 (2H, t, $J=7.4\text{Hz}$), 3.82 (3H, s), 6.47 (1H, d, $J=16.0\text{Hz}$), 7.20-7.35 (2H, m), 7.45-7.68 (6H, m), 7.73 (1H, d, $J=16.0\text{Hz}$)

APCI-MASS : $e/z = 309 (M^++1)$

Preparation 11

The following compound was obtained according to a similar manner to that of Preparation 10.

Methyl 3-(6-heptyloxynaphthalen-2-yl)acrylate

IR (Nujol) : 1716, 1625, 1459 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=6.5\text{Hz}$), 1.20-1.65- (8H, m), 1.76-1.93 (2H, m), 3.82 (3H, s), 4.07 (2H, t, $J=6.5\text{Hz}$), 6.49 (1H, d, $J=16.0\text{Hz}$), 7.05-7.20 (2H, m), 7.55-7.90 (5H, m)

APCI-MS : $e/z = 327 (M^++1)$

Preparation 12

The following compound was obtained according to a similar manner to that of Preparation 10.

Methyl 3-[4-(4-heptylphenyl)phenyl]acrylate

NMR (CDCl₃, δ) : 0.88 (3H, t, J=6.5Hz), 1.15-1.50 (8H, m), 1.50-1.75 (2H, m), 2.64 (2H, t, J=7.6Hz), 3.81 (3H, s), 6.46 (1H, d, J=16.0Hz), 7.26 (2H, d, J=8.2Hz), 7.52 (2H, d, J=8.2Hz), 7.59 (6H, s), 7.73 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 337 (M⁺+1)

Preparation 13

The following compound was obtained according to a similar manner to that of Preparation 10.

Methyl 3-[4-(4-pentyloxyphenyl)phenyl]acrylate

NMR (CDCl₃, δ) : 0.94 (3H, t, J=7.0Hz), 1.30-1.60 (4H, m), 1.70-1.93 (2H, m), 3.82 (3H, s), 4.00 (2H, t, J=6.7Hz), 6.45 (1H, d, J=16.0Hz), 6.90-7.05 (2H, m), 7.48-8.65 (6H, m), 7.72 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 325 (M⁺+1)

Preparation 14

A mixture of 6-heptyloxynaphthalen-2-carboxylic acid (1.00 g) and thionyl chloride (5 ml) was stirred for 18 hours at ambient temperature, and concentrated under reduced pressure to give crude 6-heptyloxy-2-naphthoyl chloride. To a mixture of ethyl isonipecotinate (605 mg), triethylamine (425 mg) and N,N-dimethylaminopyridine (10 mg) in dichloromethane (10 ml) was added crude 6-heptyloxy-2-naphthoyl chloride, and the mixture was stirred for 2 hours at ambient temperature, and diluted with dichloromethane. The mixture was washed with water, 1N hydrochloric acid and brine, and dried over magnesium

sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel, and eluted with (n-hexane : ethyl acetate = 3:1) to give 4-ethoxycarbonyl-1-(6-heptyloxy-2-naphthoyl)piperidine (1.20 g).

NMR (CDCl₃, δ) : 0.90 (3H, t, J=6.6Hz), 1.2-2.0 (19H, m), 2.5-2.7 (1H, m), 3.0-3.2 (2H, m), 4.1-4.3 (4H, m), 7.1-7.2 (2H, m), 7.44 (1H, dd, J=8.4 and 1.7Hz), 7.72 (1H, d, J=3.9Hz), 7.77 (1H, d, J=3.9Hz), 7.82 (1H, s)

APCI-MASS : e/z = 426 (M⁺+1)

Preparation 15

To a mixture of methyl 3,4-diaminobenzoate (1.91 g) and triethylamine (0.56 g) in N,N-dimethylformamide (20 ml) was added decanoyl chloride (2.31 g), and the mixture was stirred for an hour at 0°C. The reaction mixture was diluted with ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was dissolved in methanol (20 ml), and conc. sulfuric acid (0.05 ml) was added, and the mixture was stirred for 6 hours at 60°C. After cooling, the reaction mixture was evaporated under reduced pressure. The residue was diluted with ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel eluted with (n-hexane : ethyl acetate = 3:1) gave 5-methoxycarbonyl-2-nonylbenzimidazole (1.40 g).

IR (KBr pelet) : 2923, 1718, 1623, 1544, 1438, 1413,

1288, 1213, 1085, 750 cm^{-1}

NMR (DMSO-d_6 , δ) : 0.84 (3H, t, $J=6.7\text{Hz}$), 1.1-1.4
(12H, m), 1.7-1.9 (2H, m), 2.83 (2H, t,
 $J=7.4\text{Hz}$), 7.56 (1H, d, $J=8.4\text{Hz}$), 7.78 (1H, d,
 $J=8.4\text{Hz}$), 8.07 (1H, s)

APCI-MASS : $e/z = 303 (M^++1)$

Preparation 16

To a mixture of dimethylmalonate (4 ml), 2-hydroxy-4-octyloxybenzaldehyde (2.50 g) and piperidine (0.1 ml) in methanol (10 ml) was added acetic acid (0.01 ml), and the mixture was stirred for 3 hours at 70°C . The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate, and washed with 0.5N hydrochloric acid, water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure, and the precipitate was collected by filtration, and washed with n-hexane, and dried to give methyl 7-octyloxy coumarin-3-carboxylate (0.94 g).

NMR (DMSO-d_6 , δ) : 0.86 (3H, m), 1.2-1.6 (10H, m),
1.7-1.8 (2H, m), 3.81 (3H, s), 4.11 (2H, t,
 $J=6.4\text{Hz}$), 6.9-7.1 (2H, m), 7.83 (1H, d,
 $J=9.0\text{Hz}$), 8.75 (1H, s)

APCI-MASS : $e/z = 333 (M^++1)$

Preparation 17

To a mixture of sodium hydride (423 mg) and 4-octylphenol (2.06 g) in tetrahydrofuran (16 ml) was added dropwise ethyl 2-chloroacetoacetate at ambient temperature. The mixture was stirred for 6 hours at 70°C under nitrogen atmosphere, and poured into saturated ammonium chloride aqueous solution. The solution was extracted with ethyl acetate, and the organic layer was washed with water and brine, and dried over magnesium

sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was added to conc. H_2SO_4 (10 ml) at 0°C , and mixture was stirred for 10 minutes. The reaction mixture was poured into ice-water, and adjusted to pH 7.0 with 1N NaOH aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column-chromatography on silica gel, and eluted with (hexane : ethyl acetate = 95:5). The fractions containing the object compound were combined, and evaporated under reduced pressure to give ethyl 3-methyl 5-octylbenzo[b]furan-2-carboxylate (1.44 g).

IR (Neat) : 2925, 2854, 1712, 1596, 1463, 1292, 1149, 1089 cm^{-1}

NMR (CDCl_3 , δ) : 0.88 (3H, t, $J=6.7\text{Hz}$), 1.2-1.5 (10H, m), 1.44 (3H, t, $J=7.1\text{Hz}$), 1.6-1.8 (2H, m), 2.58 (3H, s), 2.71 (2H, t, $J=8.0\text{Hz}$), 4.45 (2H, t, $J=7.1\text{Hz}$), 7.2-7.5 (3H, m)

APCI-MASS : $e/z = 317$ (M^++1)

Preparation 18

To a solution of ethyl 3-amino-4-hydroxybenzoate (1.81 g) and triethylamine (1.53 ml) in dichloromethane (20 ml) was dropwise added decanoyl chloride (2.01 ml) at 0°C . The reaction mixture was stirred for 48 hours at ambient temperature, and washed with water, 0.5N hydrochloric acid, water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue dissolved in xylene (30 ml) was added p-toluene sulfonic acid monohydrate (0.5 g), and the mixture was stirred for 4

hours at 130°C . Ethyl acetate was added to the mixture, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel eluted with (n-hexane : ethyl acetate = 9:1, V/V) gave ethyl 2-nonyl benzo[b]oxazole-6-carboxylate (2.36 g).

IR (KBr pelet) : 2914, 1722, 1621, 1575, 1470,
1429, 1365, 1290, 1203, 1151, 1115, 1081,
1022 cm⁻¹

NMR (CDCl₃, δ) : 0.88 (3H, t, J=6.7Hz), 1.2-1.4 (12H, m), 1.42 (3H, t, J=7.2Hz), 1.90 (2H, m), 2.95 (2H, t, J=7.4Hz), 4.40 (2H, q, J=7.0Hz), 7.50 (1H, d, J=8.5Hz), 8.06 (1H, d, J=8.5Hz), 8.37. (1H, s)

APCI-MASS : e/z = 318 (M⁺+1)

Preparation 19

A mixture of methyl 3,4-diaminobenzoate (1.84 g) and 4-hexyloxy benzaldehyde (2.30 g) in nitrobenzene (40 ml) was stirred for 48 hours at 145°C. After cooling, the mixture was evaporated under reduced pressure.

Purification of the residue by column chromatography on silica gel eluted with (n-hexane : ethyl acetate = 2:1) gave 5-methoxy-carbonyl-2-(4-hexyloxyphenyl)benzimidazole (1.19 g).

NMR (CDCl₃, δ) : 0.90 (3H, t, J=6.4Hz), 1.2-1.9 (8H, m), 3.92 (3H, s), 3.90-4.1 (2H, m), 6.93 (2H, d, J=8.9Hz), 7.5-7.8 (1H, br), 7.94 (1H, dd, J=8:5 and 1.5Hz), 8.03 (1H, d, J=8.9Hz), 8.2-8.4 (1H, br)

APCI-MASS : 353 (M⁺+1)

Preparation 20

A mixture of methyl 3-[4-(4-pentylphenyl)phenyl]-acrylate (2.0 g) and 10% palladium on carbon (50% wet, 0.2 g) in tetrahydrofuran (20 ml) was stirred for 8 hours under atmospheric pressure of hydrogen at ambient temperature. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give methyl 3-[4-(4-pentylphenyl)phenyl]propionate (1.93 g).

NMR (CDCl₃, δ) : 0.90 (3H, t, J=6.8Hz), 1.25-1.50 (4H, m), 1.50-1.75 (2H, m), 2.55-2.75 (4H, m), 2.99 (2H, t, J=8.0Hz), 3.68 (3H, s), 7.10-7.30 (4H, m), 7.40-7.60 (4H, m)

APCI-MASS : e/z = 311 (M⁺+1)

Preparation 21

A mixture of methyl 3-[4-(4-pentyloxyphenyl)phenyl]-acrylate (2.70 g) and platinum oxide (0.41 g) in tetrahydrofuran (40 ml) was stirred for 8 hours under 3 atm of hydrogen at ambient temperature. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give methyl 3-[4-(4-pentyloxyphenyl)phenyl]propionate (2.70 g).

NMR (CDCl₃, δ) : 0.94 (3H, t, J=7.0Hz), 1.28-1.60 (4H, m), 1.60-1.95 (2H, m), 2.55-2.78 (2H, m), 2.98 (2H, t, J=7.8Hz), 3.98 (2H, t, J=6.5Hz), 6.85-7.05 (2H, m), 7.05-7.30 (2H, m), 7.40-7.55 (4H, m)

APCI-MASS : e/z = 327 (M⁺+1)

Preparation 22

The following compound was obtained according to a similar manner to that of Preparation 21.

Methyl 3-(6-heptyloxynaphthalen-2-yl)propionate

NMR (CDCl₃, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.70 (8H, m), 1.70-1.93 (2H, m), 2.70 (2H, t,

J=7.7Hz), 3.07 (2H, t, J=7.7Hz), 3.67 (3H, s),
4.05 (2H, t, J=6.5Hz), 7.02-7.20 (2H, m), 7.20-
7.38 (2H, m), 7.55 (1H, s), 7.66 (1H, dd, J=3.0
and 8.5Hz)

5 APCI-MASS : e/z = 329 (M^+ +1)

Preparation 23

To a mixture of methyl 3-[4-(4-pentylphenyl)phenyl]-
acrylate (0.41 g) in tetrahydrofuran (5 ml) was added 3N
10 NaOH aqueous solution (1.3 ml), and the resultant mixture
was heated to 85°C for 10 hours. The reaction mixture was
poured into a mixture of cold water and ethyl acetate, and
adjusted to about pH 2 with 6N hydrochloric acid. The
separated organic layer was washed in turn with water and
15 brine, and dried over magnesium sulfate. The magnesium
sulfate was filtered off, and the filtrate was evaporated
under reduced pressure to give 3-[4-(4-
pentylphenyl)phenyl]acrylic acid (0.41 g).

20 NMR (DMSO- d_6 , δ) : 0.87 (3H, t, J=7.5Hz), 1.15-1.46
(4H, m), 1.48-1.70 (2H, m), 2.61 (2H, t,
J=7.4Hz), 6.56 (1H, d, J=16.0Hz), 7.29 (2H, d,
J=8.2Hz), 7.60 (2H, d, J=4.0Hz), 7.66 (2H, d,
J=4.0Hz), 7.68-7.85 (3H, m)

25 APCI-MASS : e/z = 295 (M^+ +1)

Preparation 24

The following compound was obtained according to a
similar manner to that of Preparation 23.

30 3-[4-(4-pentyloxyphenyl)phenyl]propionic acid

IR (Nujol) : 1697, 1606, 1500 cm^{-1}

35 NMR (CDCl_3 , δ) : 0.94 (3H, t, J=7.1Hz), 1.25-1.60
(4H, m), 1.70-1.95 (2H, m), 2.72 (2H, t,
J=7.5Hz), 3.00 (2H, t, J=7.5Hz), 3.99 (2H, t,
J=6.5Hz), 6.95 (2H, dd, J=2.1 and 6.7Hz), 7.25

(2H, d, J=8.2Hz), 7.40-7.60 (4H, m)
APCI-MASS : e/z = 313 (M^+ +1)

Preparation 25

The following compound was obtained according to a similar manner to that of Preparation 23.

3-[4-(4-heptylphenyl)phenyl]propionic acid

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.8Hz), 1.15-1.50
(8H, m), 1.50-1.78 (2H, m), 2.65 (2H, t,
J=7.6Hz), 6.48 (1H, d, J=16.0Hz), 7.27 (2H, d,
J=8.2Hz), 7.53 (2H, d, J=8.2Hz), 7.63 (4H, m),
7.83 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 323 (M^+ +1)

Preparation 26

The following compound was obtained according to a similar manner to that of Preparation 23.

3-[4-(4-pentylphenyl)phenyl]propionic acid

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.4Hz), 1.20-1.50
(4H, m), 1.50-1.75 (2H, m), 2.64 (2H, t,
J=8.0Hz), 2.67 (2H, t, J=9.6Hz), 3.00 (2H, t,
J=8.0Hz), 7.15-7.38 (4H, m), 7.38-7.60 (4H, m)

APCI-MASS : e/z = 297 (M^+ +1)

Preparation 27

The following compound was obtained according to a similar manner to that of Preparation 23.

3-(6-heptyloxynaphthalen-2-yl)propionic acid

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.65
(8H, m), 1.75-2.00 (2H, m), 2.75 (2H, t,
J=7.7Hz), 3.09 (2H, t, J=7.7Hz), 4.06 (2H, t,
J=6.5Hz), 7.05-7.15 (2H, m), 7.15-7.35 (2H, m),

7.50-7.73 (2H, m)
APCI-MASS : $e/z = 315 (M^+ + 1)$

Preparation 28

5 The following compound was obtained according to a similar manner to that of Preparation 23.

3-(6-heptyloxynaphthalen-2-yl)acrylic acid

10 NMR ($CDCl_3$, δ) : 0.90 (3H, t, $J=6.5\text{Hz}$), 1.15-1.60 (8H, m), 1.75-1.95 (2H, m), 4.09 (2H, t, $J=6.5\text{Hz}$), 6.51 (1H, d, $J=16.0\text{Hz}$), 7.09-7.30 (2H, m), 7.65-8.00 (5H, m)

Preparation 29

15 The following compound was obtained according to a similar manner to that of Preparation 23.

3-[4-(4-Pentylphenyl)phenyl]propionic acid

20 NMR ($CDCl_3$, δ) : 0.91 (3H, t, $J=6.5\text{Hz}$), 1.23-1.50 (4H, m), 1.50-1.80 (2H, m), 2.65 (2H, t, $J=7.6\text{Hz}$), 7.27 (2H, d, $J=8.2\text{Hz}$), 7.51 (2H, d, $J=8.2\text{Hz}$), 7.58-7.80 (4H, m)

APCI-MASS : $e/z = 325 (M^+ + 1 + \text{MeOH})$

25 Preparation 30

The following compound was obtained according to a similar manner to that of Preparation 23.

3-(6-heptyloxynaphthalen-2-yl)propionic acid

30 IR (Nujol) : 2645, 2198, 1670, 1627 cm^{-1}

35 NMR ($DMSO-d_6$, δ) : 0.85 (3H, t, $J=6.5\text{Hz}$), 1.10-1.60 (8H, m), 1.65-1.90 (2H, m), 4.10 (2H, t, $J=6.5\text{Hz}$), 7.24 (1H, dd, $J=2.4$ and 8.9Hz), 7.39 (1H, d, $J=2.5\text{Hz}$), 7.55 (1H, dd, $J=1.6$ and 8.5Hz), 7.8-8.0 (2H, m), 8.22 (1H, d, $J=1.6\text{Hz}$)

APCI-MASS : $e/z = 343$ ($M^{+}+1$ + MeOH)

Preparation 31

To a solution of ethyl 3-methyl 5-octylbenzo[b]furan-2-carboxylate (1.44 g) in ethanol (20 ml) was added 10% NaOH aqueous solution (2.2 ml), and stirred for 2 hours at ambient temperature, and evaporated under reduced pressure. The residue was adjusted to pH 3.0 with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 3-methyl-5-octylbenzo[b]furan-2-carboxylic acid (1.00 g).

IR (KBr pelet) : 2923, 1689, 1664, 1581, 1456, 1319, 1159, 933 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.85 (3H, t, $J=6.7\text{Hz}$), 1.2-1.5 (10H, m), 1.5-1.8 (2H, m), 2.49 (3H, s), 2.69 (2H, t, $J=7.9\text{Hz}$), 7.32 (1H, dd, $J=8.5$ and 1.7Hz), 7.52 (1H, d, $J=8.5\text{Hz}$), 7.54 (1H, d, $J=1.7\text{Hz}$), 13.2-13.5 (1H, br)

APCI-MASS : $e/z = 289$ ($M^{+}+1$)

Preparation 32

The following compound was obtained according to a similar manner to that of Preparation 31.

3,4-dipentyloxybenzoic acid

NMR (DMSO- d_6 , δ) : 0.89 (6H, t, $J=6.8\text{Hz}$), 1.2-1.5 (8H, m), 1.6-1.8 (4H, m), 3.9-4.1 (4H, m), 7.02 (1H, d, $J=8.4\text{Hz}$), 7.43 (1H, d, $J=1.7\text{Hz}$), 7.53 (1H, dd, $J=8.4$ and 1.7Hz)

APCI-MASS : $e/z = 295$ ($M^{+}+1$)

Preparation 33

The following compound was obtained according to a similar manner to that of Preparation 31.

1-(6-heptyloxy-2-naphthoyl)piperidine-4-carboxylic acid

NMR (DMSO- d_6 , δ) : 0.88 (3H, t, $J=6.7\text{Hz}$), 1.2-2.0 (14H, m), 2.5-2.6 (1H, m), 2.9-3.2 (2H, br), 3.25 (2H, s), 4.09 (2H, t, $J=6.5\text{Hz}$), 7.20 (1H, dd, $J=8.9$ and 2.4Hz), 7.36 (1H, d, $J=2.3\text{Hz}$), 7.43 (1H, dd, $J=8.4$ and 1.5Hz), 7.8-8.0 (3H, m), 12.30 (1H, br)

APCI-MASS : $e/z = 398 (M^++1)$

Preparation 34

The following compound was obtained according to a similar manner to that of Preparation 31.

7-octyloxycoumarin-3-carboxylic acid

IR (KBr) : 1748, 1625, 1558, 1467, 1430, 1386, 1360, 1257, 1217, 1120 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.8\text{Hz}$), 1.2-1.5 (10H, m), 1.6-1.8 (2H, m), 4.11 (2H, t, $J=6.4\text{Hz}$), 6.9-7.1 (2H, m), 7.82 (1H, d, $J=8.9\text{Hz}$), 8.72 (1H, s), 12.98 (1H, br)

APCI-MASS : $e/z = 319 (M^++1)$

Preparation 35

The following compound was obtained according to a similar manner to that of Preparation 31.

4-(4-pentyloxyphenyl)cinnamic acid

IR (Nujol) : 2923, 1675, 1500, 1290, 1223, 985, 821 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.90 (3H, t, $J=7.0\text{Hz}$), 1.3-1.5 (4H, m), 1.6-1.8 (2H, m), 4.01 (2H, t, $J=6.5\text{Hz}$),

6.54 (1H, d, J=16.0Hz), 7.02 (2H, d, J=8.8Hz),
7.5-7.8 (7H, m)

APCI-MASS : e/z = 311 (M^+ +1)

5 Preparation 36

The following compound was obtained according to a similar manner to that of Preparation 31.

2-nonylbenzoxazole-6-carboxylic acid

10 NMR (DMSO- d_6 , δ) : 0.84 (3H, t, J=6.7Hz), 1.2-1.5
(12H, m), 1.7-1.9 (2H, m), 2.96 (2H, t,
J=7.4Hz), 7.76 (1H, d, J=8.4Hz), 7.98 (1H, d,
J=8.4Hz), 8.19 (1H, s)

APCI-MASS : e/z = 290 (M^+ +1)

15

Preparation 37

The following compound was obtained according to a similar manner to that of Preparation 31.

20 2-(4-hexyloxyphenyl)benzimidazole-5-carboxylic acid
NMR (DMSO- d_6 , δ) : 0.8-1.0 (3H, m), 1.3-1.6 (6H, m),
1.7-1.8 (2H, m), 4.06 (2H, t, J=6.4Hz), 7.12
(2H, d, J=8.8Hz), 7.6-7.9 (2H, m), 8.1-8.2 (3H,
m), 13.00 (1H, br)

25 APCI-MASS : e/z = 339 (M^+ +1)

Preparation 38

The following compound was obtained according to a similar manner to that of Preparation 31.

30

2-nonylbenzimidazole-5-carboxylic acid

35 NMR (DMSO- d_6 , δ) : 0.85 (3H, t, J=6.7Hz), 1.1-1.4
(12H, m), 2.7-2.9 (2H, m), 2.96 (2H, t,
J=7.6Hz), 3.6-5.2 (1H, br), 7.66 (1H, d,
J=8.4Hz), 7.90 (1H, d, J=8.4Hz), 8.15 (1H, s)

APCI-MASS : $e/z = 289 (M^{+}+1)$

Preparation 39

A solution of 4-[4-(4-octyloxyphenyl)piperazin-1-yl]benzonitrile (0.5 g) in 20% H₂SO₄ aqueous solution (30 ml) and acetic acid (20 ml) was refluxed for 9 hours. The reaction mixture was pulverized with water. The precipitate was collected by filtration, and added to a mixture of water, tetrahydrofuran and ethyl acetate, and adjusted to pH 2.5 with 1N NaOH aqueous solution. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(4-octyloxyphenyl)piperazin-1-yl]benzoic acid (388 mg).

IR (KBr) : 2929, 1664, 1600, 1510, 1240 cm⁻¹

NMR (DMSO-d₆, δ) : 0.86 (3H, t, J=6.6Hz), 1.2-1.5 (10H, m), 1.5-1.8 (2H, m), 3.13 (4H, t, J=5.3Hz), 3.44 (4H, t, J=5.3Hz), 3.88 (2H, t, J=6.5Hz), 6.83 (2H, d, J=9.2Hz), 6.94 (2H, d, J=9.2Hz), 7.02 (2H, d, J=9.0Hz), 7.79 (2H, d, J=9.0Hz)

APCI-MASS : $e/z = 411 (M^{+}+1)$

Preparation 40

To a suspension of sodium hydride (60% suspension in mineral oil) (0.296 g) in N,N-dimethylformamide (14 ml) was added 1,2,4-triazole (0.511 g) and 4-[4-(8-bromooctyloxy)phenyl]benzoic acid (1 g), and was stirred for 5 hours at 120°C. The reaction mixture was added to a mixture of water and ethyl acetate, and adjusted to pH 2.5 with conc. hydrochloric acid. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[8-(1,2,4-triazol-1-yl)octyloxy]phenyl]benzoic acid (0.81 g).

IR (KBr) : 2940, 1689, 1604, 1297, 1189 cm^{-1} .

NMR ($\text{DMSO}-d_6$, δ) : 1.1-1.53 (8H, m), 1.6-1.9 (4H, m), 4.00 (2H, t, $J=6.3\text{Hz}$), 4.16 (2H, t, $J=7.0\text{Hz}$), 7.03 (2H, d, $J=8.7\text{Hz}$), 7.67 (2H, d, $J=8.7\text{Hz}$), 7.75 (2H, d, $J=8.4\text{Hz}$), 7.95 (1H, s), 7.99 (2H, d, $J=8.4\text{Hz}$), 8.51 (1H, s), 12.9 (1H, s)

APCI-MASS : $e/z = 394 (M^++1)$

10 Preparation 41

A mixture of 2-carbamoyl-5-methoxybenzo[b]thiophene (2.0 g), acetic acid (5 ml) and 48% hydrobromic acid (20 ml) was stirred for 16 hours at 110°C , and the mixture was poured into the ice-water. The resulting precipitate was collected by filtration, and dried to give 5-hydroxybenzo[b]thiophene-2-carboxylic acid (1.66 g).

NMR ($\text{DMSO}-d_6$, δ) : 7.03 (1H, dd, $J=8.8$ and 0.6Hz), 7.31 (1H, d, $J=0.6\text{Hz}$), 7.81 (1H, d, $J=8.8\text{Hz}$), 7.96 (1H, s), 9.64 (1H, s), 13.32 (1H, s)

20 APCI-MASS : $e/z = 195 (M^++1)$

Preparation 42

25 A solution of (S)-2-tert-butoxycarbonyl-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (1 g) in a mixture of 10% NaOH aqueous solution (2.73 ml) and dimethylsulfoxide (11 ml) was stirred for half an hour at 80°C . Then, octyl bromide (0.589 ml) was added thereto, and stirred for 4 hours at 60°C . The reaction mixture was added to a mixture of water and ethyl acetate, and adjusted to pH 2.5 with conc. hydrochloric acid. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give (S)-2-tert-butoxycarbonyl-1,2,3,4-tetrahydro-7-octyloxyisoquinoline-3-carboxylic acid (1.30 g).

IR (Neat) : 2929, 1743, 1704, 1164 cm^{-1}

NMR (CDCl_3 , δ) : 0.89 (3H, t, $J=6.1\text{Hz}$), 1.1-1.6
(10H, m), 1.41 + 1.51 (9H, s, cis + trans), 1.75
(2H, quint, $J=6.5\text{Hz}$), 3.10 (2H, m), 3.90 (2H, t,
5 $J=3.9\text{Hz}$), 4.42 (1H, d, $J=16.8\text{Hz}$), 4.65 (1H, d,
 $J=16.8\text{Hz}$), 4.74 + 5.09 (1H, m, cis + trans),
6.5-6.8 (2H, m), 7.03 (1H, d, $J=8.3\text{Hz}$)

APCI-MASS : $e/z = 306$ (M^++1)-Boc

10 Preparation 43

The following compound was obtained according to a
similar manner to that of Preparation 42.

5-octyloxybenzo[b]thiophene-2-carboxylic acid

15 IR (KBr) : 1673, 1666, 1600, 1517, 1409, 1267, 1214,
1153, 865 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 1.2-1.5
(10H, m), 1.7-1.9 (2H, m), 4.02 (2H, t,
 $J=6.4\text{Hz}$), 7.13 (1H, dd, $J=8.9$ and 0.6Hz), 7.51
20 (1H, d, $J=0.6\text{Hz}$), 7.90 (1H, d, $J=9.0\text{Hz}$), 7.99
(1H, s)

APCI-MASS : $e/z = 307$ (M^++1)

Preparation 44

25 To a suspension of 1-hydroxybenzotriazole (0.283 g)
and 6-octyloxymethylpicolinic acid (0.505 g) in
dichloromethane (15 ml) was added 1-ethyl-3-(3'-
dimethylaminopropyl)carbodiimide hydrochloride ($\text{WSCD}\cdot\text{HCl}$)
(0.473 g), and stirred for 3 hours at ambient temperature.
30 The reaction mixture was poured into water. The organic
layer was taken, and dried over magnesium sulfate. The
magnesium sulfate was filtered off, and the filtrate was
evaporated under reduced pressure to give 1-(6-
octyloxymethylpicolinoyl)benzotriazole 3-oxide (737 mg).

35 IR (Neat) : 1793, 1654, 1591, 1039 cm^{-1}

Preparation 45

The following compound was obtained according to a similar manner to that of Preparation 44.

5 1-[4-(4-octyloxyphenyl)piperazin-1-yl]benzoyl]-
benzotriazole 3-oxide

IR (KBr) : 1783, 1600, 1511, 1232, 1184 cm^{-1}

10 NMR (CDCl_3 , δ) : 0.89 (3H, t, $J=6.6\text{Hz}$), 1.2-1.65
(10H, m), 1.65-1.9 (2H, m), 3.24 (4H, t,
 $J=5.3\text{Hz}$), 3.62 (4H, t, $J=5.3\text{Hz}$), 3.93 (2H, t,
 $J=6.5\text{Hz}$), 6.8-7.1 (6H, m), 7.35-7.63 (3H, m),
8.0-8.25 (3H, m)

Preparation 46

15 The following compound was obtained according to a
similar manner to that of Preparation 44.

20 1-[4-[4-[8-(1,2,4-Triazol-1-yl)octyloxy]phenyl]-
benzoyl]benzotriazole 3-oxide

IR (KBr) : 1776, 1600, 1193, 983 cm^{-1}

25 NMR (CDCl_3 , δ) : 1.2-2.0 (12H, m), 4.03 (2H, t,
 $J=6.4\text{Hz}$), 4.18 (2H, t, $J=7.1\text{Hz}$), 7.02 (2H, d,
 $J=8.7\text{Hz}$), 7.4-7.63 (3H, m), 7.63 (2H, d,
 $J=8.7\text{Hz}$), 7.79 (2H, d, $J=8.3\text{Hz}$), 7.95 (1H, s),
8.06 (1H, s), 8.12 (1H, d, $J=7.7\text{Hz}$), 8.32 (2H,
d, $J=8.3\text{Hz}$)

APCI-MASS : $e/z = 511 (M^++1)$

Preparation 47

30 The following compound was obtained according to a
similar manner to that of Preparation 44.

35 1-[2-methyl-2-(4-octyloxyphenoxy)propionyl]-
benzotriazole 3-oxide

IR (Neat) : 2927, 1810, 1504, 1047 cm^{-1}

Preparation 48

The following compound was obtained according to a similar manner to that of Preparation 44.

5 1-[2-(4-Octyloxyphenoxy)propionyl]benzotriazole
3-oxide

IR (KBr) : 2954, 1812, 1513, 1232 cm^{-1}

Preparation 49

10 The following compound was obtained according to a similar manner to that of Preparation 44.

1-[(S)-2-tert-Butoxycarbonyl-1,2,3,4-tetrahydro-7-octyloxyisoquinolin-3-ylcarbonyl]benzotriazole 3-oxide

15 IR (Neat) : 2929, 1816, 1739, 1704, 1392 cm^{-1}

Preparation 50

The following compound was obtained according to a similar manner to that of Preparation 44.

20 Succinimido 4-(4-n-octyloxyphenyl)piperazine-1-carboxylate

IR (KBr) : 2925, 1758, 1743, 1513, 1241 cm^{-1}

NMR (CDCl_3 , δ) : 0.89 (3H, t, $J=6.8\text{Hz}$), 1.2-1.5

25 (10H, m), 1.65-1.85 (2H, m), 2.83 (4H, s),

3.0-3.2 (2H, m), 3.6-3.85 (2H, m), 3.91 (2H, t,

$J=6.5\text{Hz}$), 6.84 (2H, dd, $J=8.5$ and 2.7Hz), 6.90

(2H, dd, $J=8.5$ and 2.7Hz)

APCI-MASS : $e/z = 432 (M^++1)$

Preparation 51

The following compound was obtained according to a similar manner to that of Preparation 44

35 (6-heptyloxy-2-naphthyl)methylsuccinimido carbonate

IR (KBr) : 1878, 1832, 1787, 1735, 1209 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=6.2\text{Hz}$), 1.2-1.6 (8H, m), 1.73-2.0 (2H, m), 2.83 (4H, s), 4.07 (2H, t, $J=6.5\text{Hz}$), 5.44 (2H, s), 7.13 (1H, d, $J=2.4\text{Hz}$), 7.17 (1H, dd, $J=8.8$ and 2.4Hz), 7.44 (1H, dd, $J=8.4$ and 1.6Hz), 7.67-7.85 (3H, m)

Preparation 52

The following compound was obtained according to a similar manner to that of Preparation 44.

1-(3,4-dipentyloxybenzoyl)benzotriazole 3-oxide

IR (KBr) : 2952, 1774, 1594, 1515, 1430, 1272, 1147, 1089 cm^{-1}

NMR (CDCl_3 , δ) : 0.9-1.1 (6H, m), 1.3-1.6 (8H, m), 1.8-2.1 (4H, m), 4.0-4.2 (4H, m), 6.99 (1H, d, $J=8.5\text{Hz}$), 7.4-7.6 (3H, m), 7.68 (1H, d, $J=2.0\text{Hz}$), 7.92 (1H, dd, $J=8.5$ and 2.0Hz), 8.10 (1H, d, $J=8.5\text{Hz}$)

APCI-MASS : $e/z = 412$ (M^++1)

Preparation 53

The following compound was obtained according to a similar manner to that of Preparation 44.

1-(7-octyloxycoumarin-3-yl-carbonyl)benzotriazole 3-oxide

IR (KBr) : 2925, 1754, 1716, 1610, 1548, 1282, 1199, 1172, 1139, 1064, 781, 750 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 0.86 (3H, t, $J=7.8\text{Hz}$), 1.2-1.5 (10H, m), 1.6-1.8 (2H, m), 4.11 (2H, t, $J=6.5\text{Hz}$), 6.9-7.1 (2H, m), 7.41 (1H, t, $J=7.2\text{Hz}$), 7.54 (1H, t, $J=7.2\text{Hz}$), 7.72 (1H, d, $J=8.3\text{Hz}$), 7.82 (1H, d, $J=8.3\text{Hz}$), 7.99 (1H, d, $J=8.3\text{Hz}$), 8.72 (1H, s)

APCI-MASS : $e/z = 436 (M^{+}+1)$

Preparation 54

The following compound was obtained according to a similar manner to that of Preparation 44.

1-[4-(4-pentyloxyphenyl)cinnamoyl]benzotriazole 3-oxide

IR (Nujol) : 2854, 1778, 1708, 1620, 1597, 1494,
1459, 1434, 1377, 1350, 1250, 1188, 1138, 1086,
978 cm^{-1}

Preparation 55

The following compound was obtained according to a similar manner to that of Preparation 44.

1-(5-octyloxybenzo[b]thiophen-2-ylcarbonyl)-benzotriazole 3-oxide

IR (KBr) : 2950, 1776, 1517, 1342, 1211, 1151 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 1.2-1.5 (10H, m), 1.7-1.9 (2H, m), 4.01 (2H, t, $J=6.4\text{Hz}$), 7.13 (1H, dd, $J=8.8$ and 2.4Hz), 7.42 (1H, d, $J=7.1\text{Hz}$), 7.5-7.6 (3H, m), 7.72 (1H, d, $J=8.4\text{Hz}$), 7.89 (1H, d, $J=8.8\text{Hz}$), 7.9-8.1 (2H, m)

APCI-MASS : $e/z = 424 (M^{+}+1)$

Preparation 56

The following compound was obtained according to a similar manner to that of Preparation 44.

1-(3-methyl-5-octylbenzo[b]furan-2-yl-carbonyl)-benzotriazole 3-oxide

IR (KBr) : 1776, 1575, 1469, 1363, 1324, 1276, 1114,
1027 cm^{-1}

NMR (CDCl_3 , δ) : 0.89 (3H, t, $J=6.7\text{Hz}$), 1.2-1.5

(10H, m), 2.6-2.8 (2H, m), 2.71 (3H, s), 2.76
(2H, t, J=7.4Hz), 7.4-7.6 (6H, m), 8.12 (1H, s)
APCI-MASS : 406 ($M^+ + 1$)

5 Preparation 57

The following compound was obtained according to a
similar manner to that of Preparation 44.

10 1-(2-nonylbenzoxazol 5-yl-carbonyl)benzotriazole
3-oxide

IR (KBr) : 2980, 1783, 1623, 1573, 1276, 1151, 1091,
989 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 0.84 (3H, t, J=6.8Hz), 1.1-1.4
(12H, m), 1.81 (2H, t, J=7.2Hz), 2.96 (3H, t,
J=7.4Hz), 7.41 (1H, t, J=7.0Hz), 7.54 (1H, t,
J=7.0Hz), 7.74 (2H, t, J=7.0Hz), 7.98 (2H, d,
J=7.0Hz), 8.19 (1H, s)

APCI-MASS : e/z = 407 ($M^+ + 1$)

20 Preparation 58

The following compound was obtained according to a
similar manner to that of Preparation 44.

25 1-[2-(4-hexyloxyphenyl)benzimidazol-5-yl-carbonyl]-
benzotriazole 3-oxide

IR (KBr) : 3160, 2931, 2863, 1778, 1612, 1502, 1448,
1388, 1294, 1247, 1174, 1097, 1010, 732 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 0.89 (3H, t, J=6.7Hz), 1.2-1.5
(6H, m), 1.7-1.8 (2H, m), 4.08 (2H, t, J=6.4Hz),
7.16 (2H, d, J=8.7Hz), 7.6-8.4 (9H, m), 8.3-8.6
(1H, br)

APCI-MASS : e/z = 456 ($M^+ + 1$)

Preparation 59

35 To a suspension of 1-hydroxybenzotriazole (0.20 g)

and 4-(4-pentylphenyl)cinnamic acid (0.40 g) in dichloromethane (12.0 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (0.33 g). (WSCD·HCl), and the mixture was stirred for 12 hours at ambient temperature. The reaction mixture was diluted with dichloromethane, and washed with brine, and dried over magnesium sulfate.. After magnesium sulfate was filtered off, evaporation of the filtrate and trituration with acetonitrile gave 1-[4-(4-pentylphenyl)cinnamoyl]benzotriazole 3-oxide (0.24 g).

NMR (CDCl₃, δ) : 0.91 (3H, t, J=6.6Hz), 1.20-1.50 (4H, m), 1.50-1.75 (2H, m), 2.66 (2H, t, J=8.0Hz), 7.20-8.25 (11H, m), 8.55 (1H, d, J=8.4Hz)

APCI-MASS : e/z = 412 (M⁺+1)

Preparation 60

The following compound was obtained according to a similar manner to that of Preparation 59.

1-[3-[4-(4-pentyloxyphenyl)phenyl]-2-propanoyl]-benzotriazole 3-oxide

NMR (CDCl₃, δ) : 0.90-1.05 (3H, m), 1.30-1.65 (4H, m), 1.70-1.95 (2H, m), 3.10-3.60 (4H, m), 3.90-4.10 (2H, m), 6.88-7.08 (2H, m), 7.20-8.50 (10H, m)

APCI-MASS : e/z = 430 (M⁺+1)

Preparation 61

The following compound was obtained according to a similar manner to that of Preparation 59.

1-[4-(4-heptylphenyl)cinnamoyl]benzotriazole 3-oxide

NMR (CDCl₃, δ) : 0.89 (3H, t, J=6.7Hz), 1.20-1.50 (8H, m), 1.50-1.80 (2H, m), 2.66 (2H, t,

J=7.6Hz), 6.70-8.60 (12H, m)
APCI-MASS : e/z = 440 (M^+ +1)

Preparation 62

5 The following compound was obtained according to a similar manner to that of Preparation 59.

1-[3-[4-(4-pentylphenyl)phenyl]-2-propanoyl]-
benzotriazole 3-oxide

10 NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.8Hz), 1.20-1.50
(4H, m), 1.50-1.76 (2H, m), 2.63 (2H, t,
J=7.4Hz), 3.21 (2H, t, J=7.3Hz), 3.51 (2H, t,
J=7.3Hz), 7.20-7.45 (4H, m), 7.45-7.70 (5H, m),
15 7.78 (1H, dt, J=1.0 and 7.2Hz), 8.00 (1H, d,
J=8.2Hz), 8.42 (1H, d, J=8.4Hz)
APCI-MASS : e/z = 414 (M^+ +1)

Preparation 63

20 The following compound was obtained according to a similar manner to that of Preparation 59.

1-[3-(6-heptyloxynaphthalen-2-yl)propanoyl]-
benzotriazole 3-oxide

25 NMR ($CDCl_3$, δ) : 0.80-1.10 (3H, m), 1.20-1.70 (8H,
m), 1.70-2.00 (2H, m), 3.10-3.70 (4H, m), 4.00-
4.18 (2H, m), 6.80-8.50 (10H, m)
APCI-MASS : e/z = 432 (M^+ +1)

Preparation 64

30 The following compound was obtained according to a similar manner to that of Preparation 59.

1-[3-(6-Heptyloxynaphthalen-2-yl)propenoyl]-
benzotriazole 3-oxide

35 NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.65

(8H, m), 1.75-1.95 (2H, m), 4.10 (2H, d,
J=6.5Hz), 6.75-8.62 (8H, m)
APCI-MASS : e/z = 430 (M^+ +1)

5 Preparation 65

The following compound was obtained according to a
similar manner to that of Preparation 59.

1-(4-hexylphenylbenzoyl)benzotriazole 3-oxide

10 NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=4.4Hz), 1.2-1.5 (6H,
m), 1.6-1.8 (2H, m), 2.68 (2H, t, J=8.0Hz), 7.32
(2H, d, J=8.2Hz), 7.4-7.7 (5H, m), 7.81 (2H, d,
J=6.6Hz), 8.10 (2H, d, J=8.1Hz), 8.32 (2H, d,
J=7.6Hz)

15 APCI-MASS : e/z = 400 (M^+ +1)

Preparation 66

To a solution of 4-octyloxyphenol (1 g) in
dimethylformamide (10 ml) and pyridine (0.364 ml) was
20 added N,N'-disuccinimidylcarbonate (1.16 g). The mixture
was stirred for 12 hours at ambient temperature. The
reaction mixture was added to a mixture of water and ethyl
acetate. The organic layer was taken, and dried over
magnesium sulfate. The magnesium sulfate was filtered
25 off, and the filtrate was evaporated under reduced
pressure to give 4-octyloxyphenylsuccinimidyl carbonate
(0.59 g).

IR (KBr) : 2927, 1876, 1832, 1735 cm^{-1}

30 NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.3Hz), 1.2-1.55
(10H, m), 1.67-1.87 (2H, m), 2.87 (4H, s), 3.94
(2H, t, J=6.5Hz), 6.89 (2H, d, J=9.2Hz), 7.17
(2H, d, J=9.2Hz)

APCI-MASS : e/z = 364 (M^+ +1)

The Starting Compound and the Object Compounds in the following Examples are illustrated by chemical formulae as below.

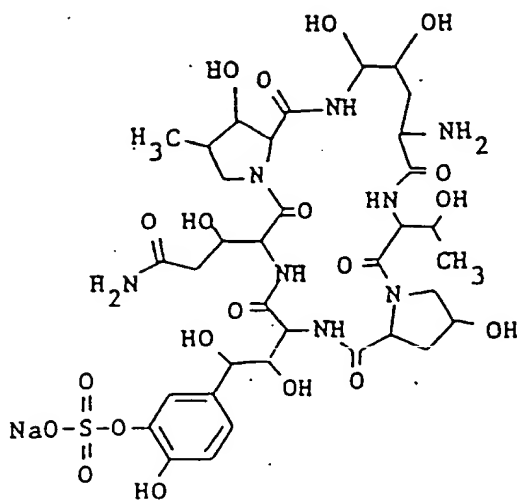
5

The Starting Compound
(the same in
all Examples)

10

15

20

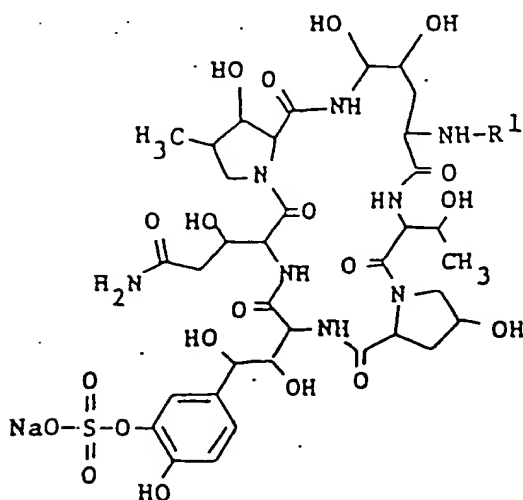


The Object Compounds

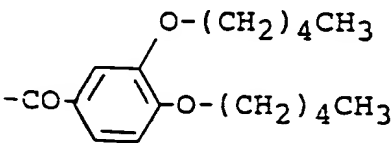
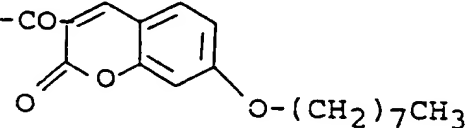
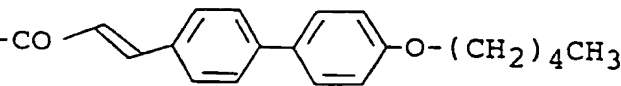
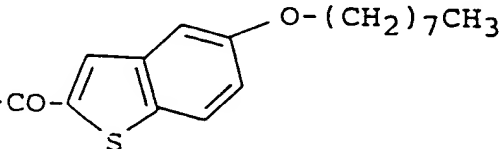
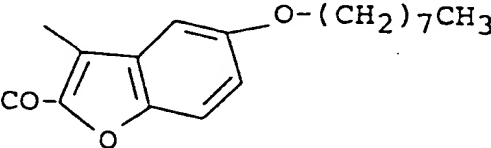
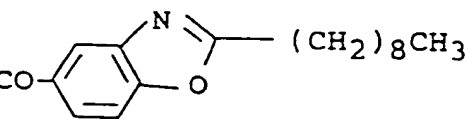
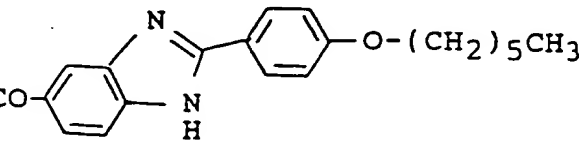
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30

35

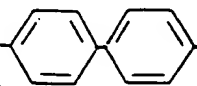
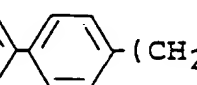


Example No.	R ¹
(1)	<chem>-CO-c1ccncc1CCOCCCCCCCC</chem>
(2)	<chem>-CO-c1ccc(cc1)N2CCN(CC2)c3ccc(cc3)OCCCCCCCC</chem>
(3)	<chem>-CO-c1ccc(cc1)-c2ccc(cc2)OCCCCCN3C=NC=N3</chem>
(4)	<chem>-CO-C(C)(C)Oc1ccc(cc1)OCCCCCCCC</chem>
(5)	<chem>-CO-CC(C)Oc1ccc(cc1)OCCCCCCCC</chem>
(6)	<chem>*C(=O)N1Cc2ccccc2Cc1ccc(OCCCCCCCC)cc1C1C(=O)OCC1</chem>
(7)	<chem>-COOc1ccc(cc1)OCCCCCCCC</chem>
(8)	<chem>-COOCCc1ccc2ccccc2c1OCCCCCCCC</chem>

Example No.	R^1
(9)	
(10)	
(11)	
(12)	
(13)	
(14)	
(15)	

Example No.	R ¹
(16)	<chem>-COCCc1ccc(cc1)-c2ccc(cc2)OCCCC</chem>
(17)	<chem>-CO/C=C/c1ccc(cc1)-c2ccc(cc2)CCCCCC</chem>
(18)	<chem>-COCCc1ccc(cc1)-c2ccc(cc2)CCCC</chem>
(19)	<chem>-CO/C=C/c1ccc(cc1)-c2ccc(cc2)CCCC</chem>
(20)	<chem>-COCCc1ccc2ccccc2c1OCCCCCC</chem>
(21)	<chem>-CO/C=C/c1ccc2ccccc2c1OCCCCCC</chem>
(22)	<chem>-COc1ccc(cc1)-c2ccc(cc2)CCCCC</chem>
(23)	<chem>-CON1CCN(CC1)c2ccc(cc2)OCCCCC</chem>

Example No.	R^1
(24)	$-\text{CO}-\text{CH}_2-\text{O}-\text{C}_6\text{H}_4-\text{O}-(\text{CH}_2)_7\text{CH}_3$
(25)	$-\text{CO}-\text{C}_6\text{H}_{10}\text{N}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{O}-(\text{CH}_2)_6\text{CH}_3$
(26)	$-\text{CO}-\text{C}_6\text{H}_3(\text{NH})=\text{N}-\text{CH}_2(\text{CH}_2)_7\text{CH}_3$
(27)	$-\text{CO}-\text{C}_5\text{H}_4\text{N}-\text{O}-(\text{CH}_2)_7\text{CH}_3$
(28)	$-\text{CO}-\text{C}\equiv\text{C}-\text{C}_{10}\text{H}_7-\text{O}-(\text{CH}_2)_6\text{CH}_3$
(29)	$-\text{CO}-\text{NH}-\text{C}_6\text{H}_4-\text{O}-(\text{CH}_2)_6\text{CH}_3$
(30)	$-\text{CO}-\text{NH}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{O}-(\text{CH}_2)_6-\text{CH}_3$

Example No.	R ¹
(31)	$\text{-CO-C}\equiv\text{C-}$  $\text{-(CH}_2\text{)}_4\text{CH}_3$
(32)	-CO-  $\text{-(CH}_2\text{)}_6\text{CH}_3$

Example 1

To a solution of The Starting Compound (1 g) and 1-(6-octyl-oxymethylpicolinoyl)benzotriazole 3-oxide (0.399 g) in N,N-dimethylformamide (10 ml) was added 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Trademark : prepared by Dow Chemical)) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50) (Trademark : prepared by Yamamura Chemical Lab.) eluting with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (1).

IR (KBr) : 3347, 1664, 1629, 1517 cm⁻¹

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 0.98 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=6.0\text{Hz}$), 1.2-1.47 (10H, m), 1.47-1.67 (2H, m), 1.67-2.06 (3H, m), 2.06-2.5 (4H, m), 3.19 (1H, m), 3.53 (2H, t, $J=6.4\text{Hz}$), 3.5-3.85 (2H, m), 3.85-4.7 (13H, m), 5.35 (11H, m), 5.56 (1H, d, $J=5.7\text{Hz}$), 6.73 (1H, d, $J=8.3\text{Hz}$), 6.83 (1H, d, $J=8.3\text{Hz}$), 6.89 (1H, s), 7.05 (1H, s), 7.11 (1H, s), 7.32 (1H, m), 7.43 (1H, d, $J=8.5\text{Hz}$), 7.63 (1H, d, $J=7.3\text{Hz}$), 7.85-8.13 (4H, m), 8.66 (1H, d, $J=7.8\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1228 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{50}H_{72}N_9O_{22}SNa \cdot 6H_2O$:

C 45.49, H 6.44, N 9.59

Found : C 45.89, H 6.52, N 9.69

Example 2

The Object Compound (2) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3353, 1666, 1510, 1236 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.06 (3H, d, $J=5.8\text{Hz}$), 1.2-1.5 (10H, m), 1.55-2.05 (5H, m), 2.11-2.7 (4H, m), 3.0-3.3 (5H, m), 3.3-3.5 (4H, m), 3.6-4.5 (15H, m), 4.6-5.6 (12H, m), 6.6-7.2 (10H, m), 7.2-7.5 (3H, m), 7.81 (2H, d, $J=8.8\text{Hz}$), 8.05 (1H, d, $J=8.7\text{Hz}$), 8.28 (1H, d, $J=8.7\text{Hz}$), 8.41 (1H, d, $J=6.7\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1373 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{60}H_{83}N_{10}O_{22}SNa \cdot 4H_2O$:

C 50.63, H 6.44, N 9.84

Found : C 50.59, H 6.59, N 9.79

Example 3

The Object Compound (3) was obtained according to a

similar manner to that of Example 1.

IR (KBr) : 3350, 1664, 1627, 1047 cm^{-1}

NMR (DMSO-d_6 , δ) : 0.96 (3H, d, $J=6.6\text{Hz}$), 1.08 (3H, d, $J=5.7\text{Hz}$), 1.15-1.53 (8H, m), 1.55-2.1 (9H, m), 2.1-2.45 (3H, m), 2.5-2.7 (1H, m), 3.18 (1H, m), 3.6-3.83 (2H, m), 3.83-4.6 (17H, m), 4.7-5.4 (11H, m), 5.51 (1H, d, $J=5.9\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.83 (1H, d, $J=8.2\text{Hz}$), 6.85 (1H, s), 7.03 (2H, d, $J=8.4\text{Hz}$), 7.05 (1H, s), 7.30 (1H, s), 7.2-7.5 (2H, m), 7.67 (2H, d, $J=8.4\text{Hz}$), 7.71 (2H, d, $J=7.4\text{Hz}$), 7.94 (1H, s), 7.96 (2H, d, $J=7.4\text{Hz}$), 8.06 (1H, d, $J=8.0\text{Hz}$), 8.25 (1H, d, $J=6.7\text{Hz}$), 8.50 (1H, s), 8.74 (1H, d, $J=6.7\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1356$ ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{76}\text{N}_{11}\text{O}_{22}\text{SNa} \cdot 4\text{H}_2\text{O}$:

C 49.53, H 6.02, N 10.95

Found : C 49.26, H 6.22, N 10.77

Example 4

The Object Compound (4) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3350, 1660, 1631, 1047 cm^{-1}

NMR (DMSO-d_6 , δ) : 0.86 (3H, t, $J=6.9\text{Hz}$), 0.97 (3H, d, $J=6.6\text{Hz}$), 1.09 (3H, d, $J=5.3\text{Hz}$), 1.2-1.5 (10H, m), 1.37 (6H, s), 1.55-2.0 (5H, m), 2.1-2.6 (4H, m), 3.16 (1H, m), 3.73 (2H, m), 3.89 (2H, t, $J=6.3\text{Hz}$), 3.95-4.49 (11H, m), 4.68-5.21 (10H, m), 5.25 (1H, d, $J=4.1\text{Hz}$), 5.53 (1H, d, $J=5.7\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.75-6.85 (4H, m), 6.91 (1H, d, $J=8.2\text{Hz}$), 7.05 (1H, s), 7.15 (1H, s), 7.3-7.5 (2H, m), 7.9-8.2 (3H, m), 8.84 (1H, s)

FAB-MASS : $e/z = 1271$ ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. For $\text{C}_{53}\text{H}_{77}\text{N}_8\text{O}_{23}\text{SNa} \cdot 4\text{H}_2\text{O}$:

C 48.18, H 6.48, N 8.48
Found : C 48.04, H 6.51, N 8.38

Example 5

The Object Compound (5) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 1666, 1629, 1222 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.85 (3H, t, $J=6.6\text{Hz}$), 0.9-1.12 (6H, m), 1.12-1.52 (13H, m), 1.52-1.93 (5H, m), 2.08-2.55 (4H, m), 3.16 (1H, m), 3.6-5.3 (26H, m), 5.49 + 5.54 (1H, d, $J=5.8\text{Hz}$, mixture of diastereomer), 6.60-7.1 (7H, m), 7.04 (1H, s), 7.1 (1H, m), 7.2-7.5 (2H, m), 7.9-8.43 (3H, m), 8.83 (1H, s)

FAB-MASS : $e/z = 1257$ ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{52}\text{H}_{75}\text{N}_8\text{O}_{23}\text{SNa} \cdot 3\text{H}_2\text{O}$:
C 48.44, H 6.33, N 8.69
Found : C 48.16, H 6.51, N 8.53

Example 6

The Object Compound (6) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3349, 1666, 1629, 1259 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 0.9 (3H, d, $J=5.7\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.1-1.55 (19H, m), 1.55-2.0 (5H, m), 2.0-2.47 (4H, m), 2.65-3.25 (3H, m), 3.5-5.13 (27H, m), 5.17 (1H, d, $J=3.2\text{Hz}$), 5.24 (1H, d, $J=4.5\text{Hz}$), 5.38 (1H, d, $J=5.9\text{Hz}$), 6.5-6.9 (5H, m), 6.9-7.1 (3H, m), 7.2-7.46 (2H, m), 7.7-8.1 (3H, m), 8.83 (1H, s)

FAB-MASS : $e/z = 1368$ ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{58}\text{H}_{84}\text{N}_9\text{O}_{24}\text{SNa} \cdot 5\text{H}_2\text{O}$:
C 48.50, H 6.60, N 8.78
Found : C 48.47, H 6.83, N 8.78

Example 7

The Object Compound (7) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3350, 1666, 1502, 1199 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.6\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.06 (3H, d, $J=5.7\text{Hz}$), 1.2-1.5 (10H, m), 1.55-2.0 (5H, m), 2.1-2.6 (4H, m), 3.17 (1H, m), 3.7-4.5 (15H, m), 4.7-5.22 (10H, m), 5.24 (1H, d, $J=4.4\text{Hz}$), 5.60 (1H, d, $J=5.9\text{Hz}$), 6.68-7.03 (8H, m), 7.04 (1H, s), 7.2-7.42 (2H, m), 7.85-8.1 (3H, m), 8.83 (1H, s)

FAB-MASS : $e/z = 1229$ ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{50}\text{H}_{71}\text{N}_8\text{O}_{23}\text{SNa} \cdot 5\text{H}_2\text{O}$:

C 46.29, H 6.29, N 8.64

Found : C 46.39, H 6.05, N 8.72

Example 8

The Object Compound (8) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3350, 1666, 1631, 1513 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.88 (3H, t, $J=6.2\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.04 (3H, d, $J=5.7\text{Hz}$), 1.2-1.58 (8H, m), 1.58-2.0 (5H, m), 2.0-2.6 (4H, m), 3.17 (1H, m), 3.6-4.5 (15H, m), 4.63-5.33 (13H, m), 5.53 (1H, d, $J=5.9\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.82 (1H, d, $J=8.2\text{Hz}$), 6.84 (1H, s), 6.95-7.52 (7H, m), 7.66 (1H, d, $J=7.6\text{Hz}$), 7.7-7.9 (3H, m), 8.05 (1H, d, $J=9.1\text{Hz}$), 8.15 (1H, d, $J=7.6\text{Hz}$), 8.85 (1H, s)

FAB-MASS : $e/z = 1279$ ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{54}\text{H}_{73}\text{N}_8\text{O}_{23}\text{SNa} \cdot 5\text{H}_2\text{O}$:

C 48.14, H 6.21, N 8.32

Found : C 48.43, H 6.28, N 8.30

Example 9

The Object Compound (9) was obtained according to a

similar manner to that of Example 1.

IR (KBr) : 3347, 2956, 1664, 1633, 1508, 1444, 1268,
1047 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.9-1.1 (9H, m), 1.06 (3H, d,
J=5.9Hz), 1.3-1.5 (8H, m), 1.6-2.0 (7H, m), 2.1-
2.4 (3H, m), 2.5-2.6 (1H, m), 3.1-3.3 (1H, m),
3.6-4.4 (17H, m), 4.7-5.0 (8H, m), 5.09 (1H, d,
J=5.5Hz), 5.16 (1H, d, J=3.1Hz), 5.24 (1H, d,
J=4.5Hz), 6.73 (1H, d, J=8.2Hz), 6.8-6.9 (2H, m),
6.98 (1H, d, J=8.3Hz), 7.05 (1H, d, J=1.7Hz), 7.3-
7.6 (5H, m), 8.08 (1H, d, J=8.9Hz), 8.25 (1H, d,
J=8.4Hz), 8.54 (1H, d, J=7.5Hz), 8.83 (1H, s)

FAB-MASS : $e/z = 1257$ ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa \cdot 4H_2O$:

C 47.78, H 6.40, N 8.57

Found : C 47.88, H 6.71, N 8.53

Example 10

The Object Compound (10) was obtained according to a
similar manner to that of Example 1.

IR (KBr) : 3350, 2931, 1664, 1625, 1529, 1440, 1276,
1226, 1047 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, J=6.8Hz), 0.97 (3H,
d, J=6.7Hz), 1.12 (3H, d, J=5.9Hz), 1.2-1.5
(10H, m), 1.6-2.1 (5H, m), 2.1-2.4 (4H, m), 3.1-
3.3 (1H, m), 3.5-4.6 (15H, m), 4.7-5.0 (3H, m),
5.0-5.2 (7H, m), 5.27 (1H, d, J=4.4Hz), 5.55
(1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.8-7.0
(2H, m), 7.0-7.2 (4H, m), 7.3-7.6 (2H, m), 7.90
(1H, d, J=8.8Hz), 8.0-8.2 (2H, m), 8.8-8.9 (2H,
m), 9.06 (1H, d, J=7.2Hz)

FAB-MASS : $e/z = 1281$ ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{53}H_{71}N_8O_{24}SNa \cdot 5H_2O$:

C 47.18, H 6.05, N 8.30

Found : C 46.97, H 6.27, N 8.22

Example 11

The Object Compound (11) was obtained according to a similar manner to that of Example 1.

NMR (DMSO- d_6 , δ) : 0.87-1.05 (6H, m), 1.10 (3H, d, J=5.7Hz), 1.3-1.5 (4H, m), 1.6-1.9 (5H, m), 2.2-2.5 (3H, m), 2.6 (1H, m), 3.1-3.2 (1H, m), 3.7-4.5 (15H, m), 4.8-5.1 (8H, m), 5.09 (1H, d, J=5.64Hz), 5.16 (1H, d, J=3.2Hz), 5.26 (1H, d, J=4.2Hz), 5.52 (1H, d, J=6.0Hz), 6.73 (2H, d, J=8.4Hz), 6.8-6.9 (2H, m), 7.0-7.1 (3H, m), 7.2-7.4 (4H, m), 7.6-7.8 (6H, m), 8.11 (1H, d, J=8.4Hz), 8.29 (1H, d, J=8.4Hz), 8.51 (1H, d, J=7.7Hz), 8.85 (1H, s)

FAB-MASS : $e/z = 1273 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{22}SNa \cdot 4H_2O$:

C 49.92, H 6.02, N 8.47

Found : C 49.79, H 6.14, N 8.45

Example 12

The Object Compound (12) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3330, 2929, 1670, 1629, 1533, 1440, 1280, 1226, 1045, 804 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.2-1.6 (10H, m), 1.6-2.0 (5H, m), 2.1-2.5 (4H, m), 3.1-3.3 (1H, m), 3.6-4.5 (15H, m), 4.8-5.1 (9H, m), 5.17 (1H, d, J=3.0Hz), 5.25 (1H, d, J=4.5Hz), 5.56 (1H, d, J=5.6Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (1H, d, J=6.8Hz), 7.1-7.2 (3H, m), 7.3-7.5 (3H, m), 7.85 (1H, d, J=8.8Hz), 8.0-8.2 (3H, m), 8.84 (1H, s), 8.96 (1H, d, J=7.2Hz)

FAB-MASS : $e/z = 1269 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{52}H_{71}N_8O_{22}S_2Na \cdot 4H_2O$:

C 47.34, H 6.04, N 8.49

Found : C 47.21, H 5.96, N 8.41

Example 13

The Object Compound (13) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3345, 2927, 1664, 1629, 1515, 1442,
1274, 1047 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.85 (3H, t, $J=6.7\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.10 (3H, d, $J=5.9\text{Hz}$), 1.2-1.4 (10H, m), 1.5-2.5 (8H, m), 2.46 (3H, s), 2.69 (2H, t, $J=7.7\text{Hz}$), 3.1-3.4 (2H, m), 3.6-4.5 (17H, m), 4.8-5.2 (8H, m), 6.7-7.0 (3H, m), 7.05 (1H, d, $J=1.7\text{Hz}$), 7.14 (1H, s), 7.3-7.6 (5H, m), 8.0-8.2 (2H, m), 8.47 (1H, d, $J=7.0\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1251$ ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{53}\text{H}_{73}\text{N}_8\text{O}_{22}\text{SNa} \cdot 3\text{H}_2\text{O}$:

C 49.61, H 6.21, N 8.73

Found : C 49.88, H 6.44, N 8.74

Example 14

The Object Compound (14) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3340, 1672, 1627, 1542, 1513, 1440, 1268,
1045 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.84 (3H, t, $J=6.7\text{Hz}$), 0.94 (3H, d, $J=6.7\text{Hz}$), 1.07 (3H, d, $J=6.0\text{Hz}$), 1.2-1.4 (12H, m), 1.6-2.0 (5H, m), 2.1-2.4 (3H, m), 2.6 (1H, m), 2.96 (2H, t, $J=7.4\text{Hz}$), 3.1-3.3 (1H, m), 3.6-4.5 (13H, m), 4.7-5.2 (11H, m), 5.50 (1H, d, $J=5.7\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.8-6.9 (2H, m), 7.04 (1H, s), 7.2-7.5 (3H, m), 7.72 (1H, d, $J=8.5\text{Hz}$), 7.91 (1H, d, $J=8.4\text{Hz}$), 8.05 (1H, d, $J=8.4\text{Hz}$), 8.2-8.4 (1H, m), 8.80 (1H, d, $J=7.7\text{Hz}$), 8.83 (1H, s)

FAB-MASS : $e/z = 1252$ ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $C_{52}H_{72}N_9O_{22}SNa \cdot 6H_2O$:

C 46.67, H 6.33, N 9.42

Found : C 46.72, H 6.53, N 9.45

5

Example 15

The Object Compound (15) was obtained according to a similar manner to that of Example 1.

10 IR (KBr) : 3350, 2935, 1664, 1627, 1517, 1446, 1251,
1045 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.90-1.1 (6H, m), 1.10 (3H, d, $J=5.9Hz$), 1.2-1.4 (6H, m), 1.6-2.4 (8H, m), 2.6-2.7 (1H, m), 3.1-3.3 (1H, m), 3.7-4.5 (16H, m), 4.7-5.4 (11H, m), 5.51 (1H, d, $J=5.6Hz$), 6.7-7.0 (3H, m), 7.0-7.6 (7H, m), 7.74 (1H, d, $J=8.6Hz$), 8.0-8.4 (5H, m), 8.7-8.8 (1H, m), 8.84 (1H, s)

15

FAB-MASS : $e/z = 1301 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{55}H_{71}N_{10}O_{22}SNa \cdot 6H_2O$:

C 47.62, H 6.03, N 10.01

20

Found : C 47.65, H 6.03, N 10.03

Example 16

The Object Compound (16) was obtained according to a similar manner to that of Example 1.

25 IR (Nujol) : 3353, 1668, 1627, 1540, 1515, 1500 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.80-1.00 (6H, m), 1.06 (3H, d, $J=5.9Hz$), 1.20-1.53 (4H, m), 1.60-1.95 (5H, m), 2.00-2.65 (8H, m), 2.80 (2H, t, $J=7.5Hz$), 3.05-3.45 (1H, m), 3.50-3.85 (2H, m), 3.90-4.48 (11H, m), 4.65-5.38 (11H, m), 5.47 (1H, d, $J=6.0Hz$), 6.65-6.90 (2H, m), 6.90-7.10 (2H, m), 7.10-7.65 (11H, m), 7.90-8.25 (2H, m), 8.30 (1H, d, $J=7.8Hz$), 8.84 (1H, s)

30

FAB-MASS : $e/z = 1275.3 (M^+ + Na)$

35

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa \cdot 3H_2O$:

C 50.53, H 6.09, N 8.57

Found : C 50.48, H 6.39, N 8.57

Example 17

5 The Object Compound (17) was obtained according to a similar manner to that of Example 1.

IR (Nujol) : 3351, 1656, 1623, 1538, 1515 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.8\text{Hz}$), 1.15-1.40 (8H, m), 1.50-2.00 (5H, m), 2.10-2.48 (4H, m); 2.52-2.70 (2H, m), 3.05-3.28 (1H, m), 3.60-4.50 (13H, m), 4.70-5.20 (9H, m), 5.25 (1H, d, $J=4.6\text{Hz}$), 5.52 (1H, d, $J=6.0\text{Hz}$), 6.68-6.92 (4H, m), 7.04 (1H, d, $J=1.0\text{Hz}$), 7.22-7.50 (5H, m), 15 7.55-7.82 (7H, m), 8.14 (1H, d, $J=8.4\text{Hz}$), 8.31 (1H, d, $J=8.4\text{Hz}$), 8.54 (1H, d, $J=7.7\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1285 (M^+ + Na)$

20 Example 18

The Object Compound (18) was obtained according to a similar manner to that of Example 1.

IR (Nujol) : 3351, 1668, 1627, 1540, 1515 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 0.87 (3H, t, $J=6.8\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.06 (3H, d, $J=5.8\text{Hz}$), 1.17-1.48 (4H, m), 1.50-1.95 (5H, m), 2.05-2.70 (8H, m), 2.70-2.95 (2H, m), 3.05-3.30 (1H, m), 3.60-3.90 (2H, m), 3.90-4.50 (11H, m), 4.65-5.10 (9H, m), 5.15 (1H, d, $J=3.2\text{Hz}$), 5.23 (1H, d, $J=4.2\text{Hz}$), 30 5.48 (1H, d, $J=6.0\text{Hz}$), 6.67-6.90 (3H, m), 7.03 (1H, d, $J=1.5\text{Hz}$), 7.15-7.80 (11H, m), 8.00-8.20 (2H, m), 8.29 (1H, d, $J=7.8\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1259 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa \cdot 6H_2O$:

35 C 50.30, H 6.52, N 8.53

Found : C 50.42, H 6.50, N 8.45

Example 19

5 The Object Compound (19) was obtained according to a similar manner to that of Example 1.

IR (Nujol) : 3351, 1668, 1652, 1623, 1540 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.87 (3H, t, $J=6.7\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.07 (3H, d, $J=6.0\text{Hz}$), 1.25-1.45 (4H, m), 1.50-2.00 (5H, m), 2.05-2.48 (4H, m), 2.50-2.75 (2H, m), 3.60-4.50 (13H, m), 4.68-5.25 (10H, m), 5.27 (1H, d, $J=4.5\text{Hz}$), 5.53 (1H, d, $J=6.0\text{Hz}$), 6.67-6.98 (4H, m), 7.05 (1H, d, $J=1.0\text{Hz}$), 7.22-7.58 (5H, m), 7.58-7.90 (7H, m), 8.16 (1H, d, $J=9.0\text{Hz}$), 8.34 (1H, d, $J=8.4\text{Hz}$), 8.57 (1H, d, $J=7.7\text{Hz}$), 8.85 (1H, s)

15 FAB-MASS : $e/z = 1258 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{21}SNa \cdot 5H_2O$:

C 49.84, H 6.15, N 8.45

20 Found : C 49.77, H 6.27, N 8.39

Example 20

The Object Compound (20) was obtained according to a similar manner to that of Example 1.

25 IR (Nujol) : 3353, 1670, 1629, 1540, 1508 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 0.88 (3H, t, $J=6.5\text{Hz}$), 0.97 (3H, d, $J=6.8\text{Hz}$), 1.04 (3H, d, $J=5.9\text{Hz}$), 1.20-1.58 (8H, m), 1.60-1.96 (5H, m), 2.08-2.60 (6H, m), 2.70-3.00 (2H, m), 3.00-3.40 (1H, m), 3.60-3.85 (2H, m), 3.85-4.50 (13H, m), 4.50-5.60 (12H, m), 6.65-6.90 (3H, m), 7.00-7.15 (3H, m), 7.18-7.50 (4H, m), 7.59 (1H, s), 7.62-7.78 (2H, m), 7.95-8.20 (2H, m), 8.30 (1H, d, $J=7.7\text{Hz}$), 8.83 (1H, s)

35 FAB-MASS : $e/z = 1277 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{55}H_{75}N_8O_{22}Na \cdot 4H_2O$:

C 49.77, H 6.30, N 8.44

Found : C 49.67, H 6.31, N 8.40

5 Example 21

The Object Compound (21) was obtained according to a similar manner to that of Example 1.

IR (Nujol) : 3351, 1654, 1623, 1538, 1515 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 0.87 (3H, t, $J=6.7Hz$), 0.97 (3H, d, $J=6.7Hz$), 1.08 (3H, d, $J=5.9Hz$), 1.20-1.58 (8H, m), 1.66-1.95 (5H, m), 2.10-2.60 (4H, m), 3.09-3.30 (1H, m), 3.58-4.60 (15H, m), 4.69-5.20 (10H, m), 5.24 (1H, d, $J=4.5Hz$), 5.51 (1H, d, $J=6.0Hz$), 6.68-6.95 (4H, m), 7.04 (1H, d, $J=1.0Hz$), 7.10-7.73 (7H, m), 7.73-7.90 (2H, m), 7.98 (1H, d, $J=1.9Hz$), 8.10 (1H, d, $J=8.4Hz$), 8.32 (1H, d, $J=8.4Hz$), 8.50 (1H, d, $J=7.7Hz$), 8.84 (1H, s)

15 FAB-MASS : $e/z = 1275 (M^+ + Na)$

20 Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}Na \cdot 5H_2O$:

C 50.38, H 6.38, N 8.55

Found : C 49.98, H 6.37, N 8.41

Example 22

25 The Object Compound (22) was obtained according to a similar manner to that of Example 1.

IR (KBr) : 3340, 2931, 1664, 1627, 1531, 1444, 1278, 1047 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.6Hz$), 0.96 (3H, d, $J=6.8Hz$), 1.08 (3H, d, $J=5.9Hz$), 1.2-1.4 (6H, m), 1.5-1.7 (2H, m), 1.7-2.1 (3H, m), 2.2-2.4 (3H, m), 2.6-2.7 (3H, m), 3.1-3.2 (1H, m), 3.7-4.6 (13H, m), 4.78 (1H, d, $J=6.0Hz$), 4.8-5.1 (1H, m), 5.09 (1H, d, $J=5.6Hz$), 5.16 (1H, d, $J=3.2Hz$), 5.24 (1H, d, $J=4.4Hz$), 5.52 (1H, d,

J=6.0Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (2H, d, J=8.3Hz), 7.05 (1H, s), 7.3-7.5 (5H, m), 7.65 (2H, d, J=8.2Hz), 7.74 (2H, d, J=8.4Hz), 7.98 (2H, d, J=8.4Hz), 8.11 (1H, d, J=8.4Hz), 8.31 (1H, d, J=8.4Hz), 8.79 (1H, d, J=7.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1245 (M⁺+Na)

Elemental Analysis Calcd. for C₅₄H₇₁N₈O₂₁SNa·4H₂O :

C 50.07, H 6.15, N 8.65

Found : C 50.26, H 6.44, N 8.67

Example 23

To a solution of The Starting Compound (1 g) and succinimido 4-(4-octyloxyphenyl)piperazine-1-carboxylate (0.45 g) in N,N-dimethylformamide (10 ml) was added 4-dimethylaminopyridine (0.141 g), and stirred for 5 days at 50°C. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give crude The Object Compound (23). The powder of crude The Object Compound (23) was purified by preparative HPLC utilizing a C₁₈ μ Bondapak resin (Waters Associates, Inc.) which was eluted with a solvent system comprised of (acetonitrile-pH 3 phosphate buffer = 40:60) at a flow rate of 80 ml/minute using a Shimadzu LC-8A pump. The column was monitored by a UV detector set at 240 nm. The fractions containing the object compound were combined,

and evaporated under reduced pressure to remove acetonitrile. The residue was subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (23) (60 mg).

IR (KBr) : 3347, 1629, 1511, 1245 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 0.95 (3H, d, $J=6.8\text{Hz}$), 1.06 (3H, d, $J=5.9\text{Hz}$), 1.2-1.5 (10H, m), 1.55-1.92 (5H, m), 2.0-2.65 (4H, m), 2.8-3.05 (5H, m), 3.2-4.47 (17H, m), 4.6-5.6 (12H, m), 6.6-7.0 (7H, m), 7.03 (1H, s), 7.2-7.5 (3H, m), 7.9-8.3 (3H, m), 8.84 (1H, s)

FAB-MASS : $e/z = 1297$ ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{54}\text{H}_{79}\text{N}_{10}\text{O}_{22}\text{SNa} \cdot 6\text{H}_2\text{O} \cdot \text{CH}_3\text{CN}$:

C 47.22, H 6.65, N 10.82

Found : C 47.58, H 7.05, N 10.85

Example 24

To a suspension of 1-hydroxybenzotriazole (0.53 g) and 2-(4-octyloxyphenoxy)acetic acid (1 g) in dichlormethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.886 g), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[2-(4-octyloxyphenoxy)acetyl]benzotriazole 3-oxide (892 mg). To a solution of 1-[2-(4-octyloxyphenoxy)acetyl]benzotriazole 3-oxide (892 mg) in N,N-dimethylformamide (18 ml) was

added 4-(N,N-dimethylamino)pyridine (0.297 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was added to water, and subjected to ion-exchange column chromatography on DOWEX-50WX4, and eluted with water. The fractions containing the object compound were combined, and subjected to column chromatograph on ODS (YMC-gel.ODS-AM-S-50), and eluted with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (24) (1.75 g).

IR (KBr) : 3350, 1666, 1629, 1228 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.9\text{Hz}$), 0.95 (3H, d, $J=6.7\text{Hz}$), 1.04 (3H, d, $J=5.7\text{Hz}$), 1.15-1.5 (10H, m), 1.55-2.0 (5H, m), 2.05-2.5 (4H, m), 3.16 (1H, m), 3.72 (2H, m), 3.88 (3H, t, $J=6.3\text{Hz}$), 4.41 (2H, s), 3.93-4.6 (11H, m), 4.69-5.25 (10H, m), 5.28 (1H, d, $J=4.3\text{Hz}$), 5.57 (1H, d, $J=5.7\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.8-7.0 (5H, m), 7.04 (1H, s), 7.09 (1H, s), 7.3-7.4 (2H, m), 7.92-8.17 (2H, m), 8.29 (1H, d, $J=7.5\text{Hz}$), 8.84 (1H, s)

FAB-MASS : $e/z = 1243$ ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{51}H_{73}N_8O_{23}SNa \cdot 4H_2O$:
C 47.36, H 6.31, N 8.66
Found : C 47.22, H 6.44, N 8.37

Example 25

The Object Compound (25) was obtained according to a similar manner to that of Example 24.

IR (KBr) : 3350, 2933, 1664, 1628, 1446, 1205, 1045 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.8-1.1 (9H, m), 1.2-2.0 (19H,

m), 2.1-2.3 (3H, m), 3.6-3.8 (4H, m), 3.9-4.4 (13H, m), 4.6-5.0 (8H, m), 5.07 (1H, d, J=5.6Hz), 5.14 (1H, d, J=3.2Hz), 5.23 (1H, d, J=4.3Hz), 5.46 (1H, d, J=6.7Hz), 6.7-6.9 (3H, m), 7.04 (1H, s), 7.2-7.5 (6H, m), 7.8-8.0 (3H, m), 8.05 (1H, d, J=8.4Hz), 8.2-8.4 (2H, m), 8.83 (1H, s)

FAB-MASS : $e/z = 1360 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{59}H_{80}N_9O_{23}SNa \cdot 6H_2O$:

C 48.99, H 6.41, N 8.72

Found : C 48.92, H 6.37, N 8.64

Example 26

The Object Compound (26) was obtained according to a similar manner to that of Example 24.

IR (KBr) : 3350, 2927, 1668, 1627, 1535, 1515, 1452, 1440, 1286, 1045 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.83 (3H, t, J=6.7Hz), 0.95 (3H, d, J=6.7Hz), 1.07 (3H, d, J=5.9Hz), 1.2-1.4 (12H, m), 1.6-2.0 (5H, m), 2.1-2.4 (3H, m), 2.6 (1H, m), 2.82 (2H, t, J=7.4Hz), 3.1-3.2 (1H, m), 3.6-4.5 (13H, m), 4.7-5.2 (11H, m), 5.4-5.6 (1H, m), 6.72 (1H, d, J=8.2Hz), 6.82 (2H, d, J=8.1Hz), 7.03 (1H, s), 7.2-7.4 (3H, m), 7.47 (1H, d, J=8.5Hz), 7.69 (1H, d, J=8.5Hz), 8.1-8.2 (2H, m), 8.23 (1H, d, J=8.4Hz), 8.62 (1H, d, J=7.8Hz), 8.83 (1H, s)

FAB-MASS : $e/z = 1251 (M^+ + Na)$

Elemental Analysis Calcd. for $C_{52}H_{73}N_{10}O_{21}SNa \cdot 5H_2O$:

C 47.34, H 6.34, N 10.61

Found : C 47.30, H 6.45, N 10.45

Example 27

The Object Compound (27) was obtained according to a similar manner to that of Example 24.

NMR (DMSO- d_6 , δ) : 0.86 (3H, t, $J=6.8\text{Hz}$), 0.96 (3H, t, $J=6.7\text{Hz}$), 1.05 (3H, t, $J=5.8\text{Hz}$), 1.2-1.5 (10H, m), 1.6-2.0 (5H, m), 2.2-2.4 (3H, m), 2.5-2.6 (1H, m), 3.1-3.2 (1H, m), 3.7-4.5 (15H, m), 4.7-5.0 (8H, m), 5.10 (1H, d, $J=5.6\text{Hz}$), 5.17 (1H, d, $J=3.1\text{Hz}$), 5.26 (1H, d, $J=4.5\text{Hz}$), 5.52 (1H, d, $J=5.8\text{Hz}$) 6.73 (1H, d, $J=8.2\text{Hz}$), 6.8-7.0 (3H, m), 7.04 (1H, s), 7.2-7.4 (3H, m), 8.0-8.3 (3H, m), 8.68 (1H, d, $J=2.3\text{Hz}$), 8.7-8.8 (1H, m), 8.85 (1H, m)

FAB-MASS : $e/z = 1214$ ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{49}H_{70}N_9O_{22}SNa \cdot 4H_2O$:

C 46.55, H 6.22, N 9.97

Found : C 46.29, H 6.18, N 9.71

Example 28

The Object Compound (28) was obtained according to a similar manner to that of Example 24.

IR (Nujol) : 3342, 2210, 1668, 1623 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.88 (3H, t, $J=6.7\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=6.7\text{Hz}$), 1.20-1.60 (8H, m), 1.60-2.00 (5H, m), 2.05-2.50 (4H, m), 3.05-3.30 (1H, m), 3.60-4.60 (15H, m), 4.65-5.18 (10H, m), 5.24 (1H, d, $J=4.5\text{Hz}$), 5.58 (1H, d, $J=6.0\text{Hz}$), 6.68-7.10 (4H, m), 7.15-7.65 (5H, m), 7.80-8.30 (6H, m), 8.84 (1H, s), 9.18 (1H, d, $J=7.7\text{Hz}$)

FAB-MASS : $e/z = 1273.5$ ($M^+ + Na$)

Example 29

To a solution of 6-heptyloxy-2-naphthoic acid (0.358 g) and triethylamine (0.174 ml) in N,N -dimethylformamide (10 ml) was added diphenylphosphoryl azide (0.4 ml), and stirred for an hour at ambient temperature. Then, the reaction mixture was stirred for an hour at 100°C . After

cooling, to the reaction mixture was added The Starting Compound (1 g) and 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 10 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate.

5 The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined,
10 and subjected to column chromatography on ODS (YMC-gel-ODS-AM-S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give
15 The Object Compound (29) (0.832 g).

IR (KBr) : 3350, 1664, 1629, 1546, 1240 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.88 (3H, t, $J=6.6\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.9\text{Hz}$), 1.2-1.55 (8H, m), 1.55-2.0 (5H, m), 2.1-2.5 (4H, m),
20 3.18 (1H, m), 3.6-3.8 (3H, m), 3.9-4.5 (13H, m), 4.7-4.95 (3H, m), 5.0-5.3 (7H, m), 5.59 (1H, d, $J=5.8\text{Hz}$), 6.52 (1H, d, $J=8.1\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.83 (1H, d, $J=8.2\text{Hz}$), 6.90 (1H, s),
25 7.0-7.15 (3H, m), 7.20 (1H, s), 7.27-7.4 (3H, m), 7.6-7.7 (2H, m), 7.87 (1H, s), 7.95-8.2 (2H, m), 8.69 (1H, s), 8.85 (1H, s)

FAB-MS : $e/z = 1264$ ($M^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{53}\text{H}_{72}\text{N}_9\text{O}_{22}\text{SNa} \cdot 5\text{H}_2\text{O}$:

C 47.78, H 6.20, N 9.46

30 Found : C 47.65, H 6.42, N 9.34

Example 30

The Object Compound (30) was obtained according to a similar manner to that of Example 29.

35 IR (KBr) : 3350, 1666, 1629, 1537, 1240 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.87 (3H, t, $J=6.7\text{Hz}$), 0.97 (3H, d, $J=6.7\text{Hz}$), 1.09 (3H, d, $J=5.8\text{Hz}$), 1.2-1.55 (8H, m), 1.55-2.0 (5H, m), 2.07-2.6 (4H, m), 3.18 (1H, m), 3.6-3.85 (3H, m), 3.9-4.5 (13H, m), 4.7-4.98 (3H, m), 5.0-5.3 (7H, m), 5.57 (1H, d, $J=5.9\text{Hz}$), 6.50 (1H, d, $J=8.1\text{Hz}$), 6.73 (1H, d, $J=8.2\text{Hz}$), 6.82 (1H, dd, $J=8.2$ and 1.7Hz), 6.87 (1H, s), 6.97 (2H, d, $J=8.8\text{Hz}$), 7.05 (1H, d, $J=1.7\text{Hz}$), 7.10 (1H, s), 7.23-7.43 (2H, m), 7.38 (2H, d, $J=8.8\text{Hz}$), 7.50 (2H, d, $J=8.8\text{Hz}$), 7.52 (2H, d, $J=8.8\text{Hz}$), 8.0-8.15 (2H, m), 8.65 (1H, s), 8.84 (1H, s)

FAB-MASS : $e/z = 1290$ ($M^+ + Na$)

Elemental Analysis Calcd. for $C_{55}H_{74}N_9O_{22}SNa \cdot 7H_2O$:

C 47.38, H 6.36, N 9.04

Found : C 47.67, H 6.53, N 9.03

Example 31

A solution of The Starting Compound (2.45 g), 3-[4-(4-pentylphenyl)phenyl]propionic acid (0.90 g), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.59 g) and triethylamine (0.43 ml) in N,N-dimethylformamide (50 ml) was stirred for 15 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate, and the resultant precipitate was collected by filtration, and washed in turn with ethyl acetate and diisopropyl ether, and dried under reduced pressure. The powder was dissolved in water, and was subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Na form, 50 ml)) eluting with water. The fractions containing the object compound were combined, and subjected to reversed phase chromatography on ODS (YMC-gel-ODS-AM-S-50, 50 ml) eluting with (water : acetonitrile = 10:0 - 7:3, V/V). The fractions containing the object compound were combined, and evaporated under

reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (31) (1.53 g).

IR (Nujol) : 3351, 2212, 1668, 1627 cm^{-1}

5 NMR (DMSO-d_6 , δ) : 0.87 (3H, t, $J=6.5\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.8\text{Hz}$), 1.20-1.50 (4H, m), 1.50-2.00 (5H, m), 2.03-2.55 (4H, m), 2.62 (2H, t, $J=7.5\text{Hz}$), 3.17 (1H, t, $J=8.4\text{Hz}$), 3.55-4.57 (15H, m), 4.65-5.13 (9H, m), 5.16 (1H, d, $J=3.2\text{Hz}$), 5.24 (1H, d, $J=4.5\text{Hz}$), 5.58 (1H, d, $J=5.8\text{Hz}$), 6.67-6.90 (3H, m), 6.93-7.10 (2H, m), 7.15-7.50 (4H, m), 7.50-7.90 (6H, m), 8.06 (1H, d, $J=8.4\text{Hz}$), 8.15 (1H, d, $J=7.7\text{Hz}$), 8.84 (1H, s), 9.19 (1H, d, $J=7.1\text{Hz}$)

10 FAB-MASS : $e/z = 1255$ ($\text{M}^+ + \text{Na}$)

15 Elemental Analysis Calcd. for $\text{C}_{55}\text{H}_{69}\text{N}_8\text{O}_{21}\text{SNa} \cdot 4\text{H}_2\text{O}$:

C 50.61, H 5.95, N 8.58

Found : C 50.47, H 6.00, N 8.54

Example 32

20 To a suspension of 1-hydroxybenzotriazole (501 mg) and 4-(4-heptylphenyl)benzoic acid (1 g) in dichloromethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride ($\text{WSCD} \cdot \text{HCl}$) (839 mg), and stirred for 3 hours at ambient temperature.

25 The reaction mixture was added to water. The organic layer was separated, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[4-(4-heptylphenyl)benzoyl]benzotriazole 3-oxide. To a solution

30 of The Starting Compound (2.49 g) and 1-[4-(4-heptylphenyl)benzoyl]benzotriazole 3-oxide in N,N -dimethylformamide (25 ml) was added 4-(N,N -dimethylamino)pyridine (381 mg), and stirred for 12 hours at ambient temperature. The reaction mixture was

35 pulverized with ethyl acetate. The precipitate was

collected by filtration, and dried under reduced pressure. The residue was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fraction containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel.ODS-AM.S-50) eluting with 30% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (32) (1.99 g).

IR (Nujol) : 3350, 2852, 1749, 1621, 1457, 1376, 1045 cm^{-1}

NMR (DMSO-d_6 , δ) : 0.86 (3H, t, $J=6.7\text{Hz}$), 0.96 (3H, d, $J=6.7\text{Hz}$), 1.08 (3H, d, $J=5.9\text{Hz}$), 1.5-1.7 (2H, m), 1.7-2.2 (3H, m), 2.2-2.5 (3H, m), 2.6-2.8 (3H, m), 3.1-3.2 (1H, m), 3.7-4.6 (13H, m), 4.7-5.2 (8H, m), 5.12 (1H, d, $J=5.5\text{Hz}$), 5.18 (1H, d, $J=2.9\text{Hz}$), 5.27 (1H, d, $J=4.4\text{Hz}$), 5.54 (1H, d, $J=5.8\text{Hz}$), 6.7-6.9 (3H, m), 7.05 (1H, s), 7.2-7.4 (5H, m), 7.65 (2H, d, $J=8.0\text{Hz}$), 7.74 (2H, d, $J=8.3\text{Hz}$), 7.98 (2H, d, $J=8.3\text{Hz}$), 8.11 (1H, d, $J=8.7\text{Hz}$), 8.28 (1H, d, $J=8.4\text{Hz}$), 8.78 (1H, d, $J=7.3\text{Hz}$), 8.85 (1H, s)

FAB-MASS : $e/z = 1259$ ($\text{M}^+ + \text{Na}$)

Elemental Analysis Calcd. for $\text{C}_{55}\text{H}_{73}\text{N}_8\text{O}_{21}\text{SNa} \cdot 5\text{H}_2\text{O}$:

C 49.77, H 6.30, N 8.44

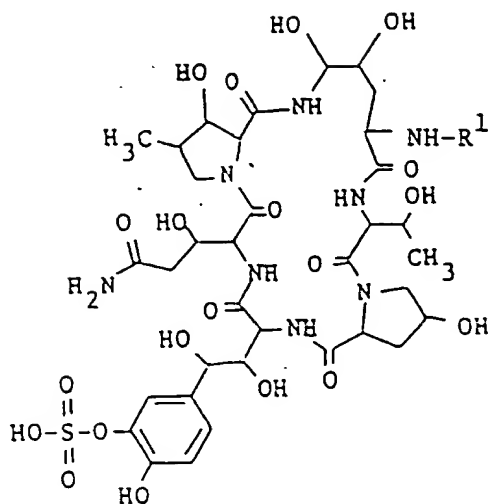
Found : C 49.98, H 6.44, N 8.41

What we claim is :

1. A polypeptide compound of the following general formula :

5

10



[I]

15

wherein R¹ is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

20

lower alkanoyl substituted with
1,2,3,4-tetrahydroisoquinoline which
may have one or more suitable
substituent(s);

25

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

30

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable

35

substituent(s);

lower alkanoyl substituted with
unsaturated condensed heterocyclic
group containing 2 or more nitrogen
atom(s) which may have one or more
suitable substituent(s);

lower alkanoyl substituted with
saturated 3 to 8-membered
heteromonocyclic group containing at
least one nitrogen atom which may have
one or more suitable substituent(s);

ar(lower)alkenoyl substituted with
aryl which may have one or more
suitable substituent(s);

naphthyl(lower)alkenoyl which may
have one or more higher alkoxy;

lower alkynoyl which may have one or
more suitable substituent(s);

ar(C₂-C₆)alkanoyl substituted with
aryl having one or more suitable
substituent(s);

(C₂-C₆)alkanoyl substituted with
naphthyl having higher alkoxy;

aroyl substituted with heterocyclic
group which may have one or more
suitable substituent(s);

aroyl substituted with aryl having
heterocyclic(higher)alkoxy;

aroyl substituted with 2 lower
alkoxy;

aroyl substituted with aryl having
lower alkyl;

aroyl substituted with aryl having
higher alkyl;

aryloxy(lower)alkanoyl which may have

one or more suitable substituent(s);
ar(lower)alkoxy(lower)alkanoyl which
may have one or more suitable
substituent(s);

5 arylamino(lower)alkanoyl which may
have one or more suitable
substituent(s); and

a pharmaceutically acceptable salt thereof.

10 2. A compound of claim 1, wherein

R¹ is lower alkanoyl substituted with unsaturated 6-
membered heteromonocyclic group containing at
least one nitrogen atom which may have 1 to 3
substituent(s) selected from the group consisting
15 of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
higher alkoxy, phenyl having lower alkyl, phenyl
20 having higher alkyl, naphthoyl having higher
alkoxy, phenyl substituted with phenyl having
lower alkyl, and oxo;

lower alkanoyl substituted with 1,2,3,4-
tetrahydroisoquinoline having higher alkoxy and
25 lower alkoxy carbonyl;

lower alkanoyl substituted with unsaturated
condensed heterocyclic group containing at least
one oxygen atom which may have 1 to 3
substituent(s) selected from the group consisting
30 of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
higher alkoxy, phenyl having lower alkyl, phenyl
35 having higher alkyl, naphthoyl having higher

alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

5 lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, 10 naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

15 lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atoms which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, 20 higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher 25 alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 30 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having 35 higher alkoxy, phenyl having lower alkyl, phenyl

having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

3. A compound of claim 1, wherein

R^1 is ar(lower)alkenoyl substituted with aryl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

ar(C₂-C₆)alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having

higher alkoxy, phenyl substituted with phenyl
having lower alkyl, and oxo;

(C₂-C₆)alkanoyl substituted with naphthyl having
higher alkoxy.

5

4. A compound of claim 1, wherein

R¹ is aroyl substituted with heterocyclic group which
may have 1 to 3 substituent(s) selected from the
group consisting of lower alkoxy, higher alkoxy,
10 lower alkyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
having lower alkyl, phenyl having higher alkyl,
15 naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

aroyl substituted with aryl having
heterocyclic(higher)alkoxy;

aroyl substituted with 2 lower alkoxy;

20 aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl.

5. A compound of claim 1, wherein

R¹ is aryloxy(lower)alkanoyl which may have 1 to 3
25 substituent(s) selected from the group consisting
of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
30 higher alkoxy, phenyl having lower alkyl, phenyl
having higher alkyl, naphthoyl having higher
alkoxy, phenyl substituted with phenyl having
lower alkyl, and oxo.

35

6. A compound of claim 1, wherein

R¹ is ar(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

7. A compound of claim 1, wherein

R¹ is arylamino(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

8. A compound of claim 2, wherein

R¹ is lower alkanoyl substituted with pyridyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with 1,2,3,4-

tetrahydroisoquinoline having higher alkoxy and lower alkoxy carbonyl;

5 lower alkanoyl substituted with coumarine which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl
10 having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

15 lower alkanoyl substituted with benzothiophenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl
20 having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

25 lower alkanoyl substituted with benzo[b]furanyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl
30 having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

35 lower alkanoyl substituted with benzooxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher

alkoxy, lower alkyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
5 having lower alkyl, phenyl having higher alkyl,
naphthyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with benzimidazolyl
which may have 1 to 3 substituent(s) selected from
10 the group consisting of lower alkoxy, higher
alkoxy, lower alkoyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
15 having lower alkyl, phenyl having higher alkyl,
naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with saturated
6-membered heteromonocyclic group containing at
20 least one nitrogen atom which may have 1 to 3
substituent(s) selected from the group consisting
of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
25 naphthyl having lower alkoxy, naphthyl having
higher alkoxy, phenyl having lower alkyl, phenyl
having higher alkyl, naphthoyl having higher
alkoxy, phenyl substituted with phenyl having
lower alkyl, and oxo.

30 9. A compound of claim 3, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl
which may have 1 to 3 substituent(s) selected from
the group consisting of lower alkoxy, higher
35 alkoxy, lower alkyl, higher alkyl, higher

alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
having lower alkyl, phenyl having higher alkyl,
5 naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkenoyl substituted with phenyl
which may have 1 to 3 substituent(s) selected from
the group consisting of lower alkoxy, higher
10 alkoxy, lower alkyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
having lower alkyl, phenyl having higher alkyl,
15 naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkenoyl which may have 1 to 3
higher alkoxy;

lower alkynoyl which may have 1 to 3
20 substituent(s) selected from the group consisting
of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
25 higher alkoxy, phenyl having lower alkyl, phenyl
having higher alkyl, phenyl substituted with
phenyl having lower alkoxy, phenyl substituted
with phenyl having higher alkoxy, naphthyl
substituted with phenyl having lower alkoxy,
30 naphthyl substituted with phenyl having higher
alkoxy, naphthoyl having higher alkoxy, phenyl
substituted with phenyl having lower alkyl, and
oxo;

phenyl(C₂-C₆)alkanoyl substituted with phenyl
35 which has 1 to 3 substituent(s) selected from the

group consisting of lower alkoxy, higher alkoxy,
lower alkyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
having lower alkyl, phenyl having higher alkyl,
naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

naphthyl(C₂-C₆)alkanoyl substituted with phenyl
which may have 1 to 3 substituent(s) selected from
the group consisting of lower alkoxy, higher
alkoxy, lower alkyl, higher alkyl, higher
alkoxy(lower)alkyl, phenyl having lower alkoxy,
phenyl having higher alkoxy, naphthyl having lower
alkoxy, naphthyl having higher alkoxy, phenyl
having lower alkyl, phenyl having higher alkyl,
naphthoyl having higher alkoxy, phenyl substituted
with phenyl having lower alkyl, and oxo;

(C₂-C₆)alkanoyl substituted with naphthyl having
higher alkoxy.

10. A compound of claim 4, wherein

R¹ is benzoyl substituted with saturated 6-membered
heteromonocyclic group containing at least one
nitrogen atom which may have 1 to 3 substituent(s)
selected from the group consisting of lower
alkoxy, higher alkoxy, lower alkyl, higher alkyl,
higher alkoxy(lower)alkyl, phenyl having lower
alkoxy, phenyl having higher alkoxy, naphthyl
having lower alkoxy, naphthyl having higher
alkoxy, phenyl having lower alkyl, phenyl having
higher alkyl, naphthoyl having higher alkoxy,
phenyl substituted with phenyl having lower alkyl,
and oxo;

naphthoyl substituted with saturated 6-membered

heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

benzoyl substituted with phenyl having unsaturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom substituted with higher alkoxy;

benzoyl substituted with 2 lower alkoxy;

benzoyl substituted with phenyl having lower alkyl;

naphthoyl substituted with phenyl having lower alkyl;

benzoyl substituted with phenyl having higher alkyl;

naphthoyl substituted with phenyl having higher alkyl.

11. A compound of claim 5, wherein

R¹ is phenyloxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having

lower alkyl, and oxo;

napthyloxy(lower)alkanoyl which may have 1 to 3
substituent(s) selected from the group consisting
of lower alkoxy, higher alkoxy, lower alkyl,
5 higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
higher alkoxy, phenyl having lower alkyl, phenyl
having higher alkyl, naphthoyl having higher
10 alkoxy, phenyl substituted with phenyl having
lower alkyl, and oxo.

12. A compound of claim 6, wherein

R¹ is phenyl(lower)alkoxy(lower)alkanoyl which may
15 have 1 to 3 substituent(s) selected from the group
consisting of lower alkoxy, higher alkoxy, lower
alkyl, higher alkyl, higher alkoxy(lower)alkyl,
phenyl having lower alkoxy, phenyl having higher
alkoxy, naphthyl having lower alkoxy, naphthyl
20 having higher alkoxy, phenyl having lower alkyl,
phenyl having higher alkyl, naphthoyl having
higher alkoxy, phenyl substituted with phenyl
having lower alkyl, and oxo;

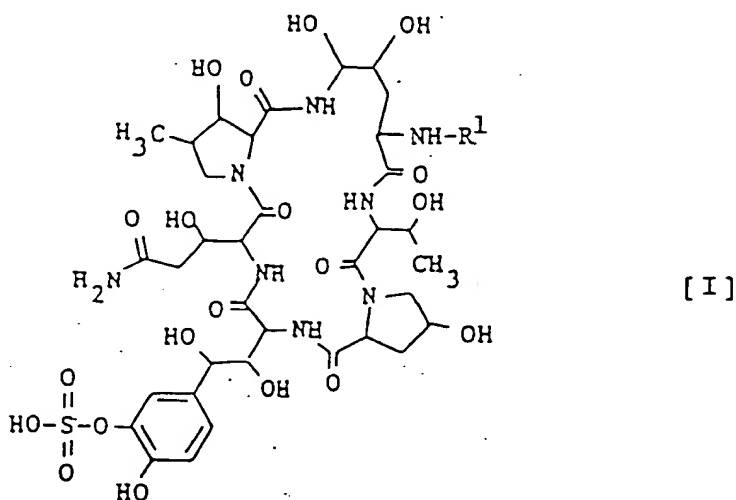
naphthyl(lower)alkoxy(lower)alkanoyl which may
25 have 1 to 3 substituent(s) selected from the group
consisting of lower alkoxy, higher alkoxy, lower
alkyl, higher alkyl, higher alkoxy(lower)alkyl,
phenyl having lower alkoxy phenyl having higher
alkoxy, naphthyl having lower alkoxy, naphthyl
30 having higher alkoxy, phenyl having lower alkyl,
phenyl having higher alkyl, naphthoyl having
higher alkoxy, phenyl substituted with phenyl
having lower alkyl, and oxo;

phenylamino(lower)alkanoyl which may have 1 to 3
35 substituent(s) selected from the group consisting

of lower alkoxy, higher alkoxy, lower alkyl,
higher alkyl, higher alkoxy(lower)alkyl, phenyl
having lower alkoxy, phenyl having higher alkoxy,
naphthyl having lower alkoxy, naphthyl having
higher alkoxy, phenyl having lower alkyl, phenyl
having higher alkyl, naphthoyl having higher
alkoxy, phenyl substituted with phenyl having
lower alkyl, and oxo;

naphthylamino(lower)alkanoyl which may have 1 to
3 substituent(s) selected from the group
consisting of lower alkoxy, higher alkoxy, lower
alkyl, higher alkyl, higher alkoxy(lower)alkyl,
phenyl having lower alkoxy phenyl having higher
alkoxy, naphthyl having lower alkoxy, naphthyl
having higher alkoxy, phenyl having lower alkyl,
phenyl having higher alkyl, naphthoyl having
higher alkoxy, phenyl substituted with phenyl
having lower alkyl, and oxo.

13. A process for the preparation of a polypeptide
compound of the formula [I] :



wherein R^1 is lower alkanoyl substituted with
unsaturated 6-membered heteromonocyclic

group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydro-isoquinoline having higher alkoxy;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

ar(C₂-C₆)alkanoyl substituted with aryl having one or more suitable

substituent(s);

(C₂-C₆)alkanoyl substituted with
naphthyl having higher alkoxy;

5 aroyl substituted with heterocyclic
group which may have one or more
suitable substituent(s);

aroyl substituted with aryl having
heterocyclic(higher)alkoxy;

10 aroyl substituted with 2 lower
alkoxy;

aroyl substituted with aryl having
lower alkyl;

aroyl substituted with aryl having
higher alkyl;

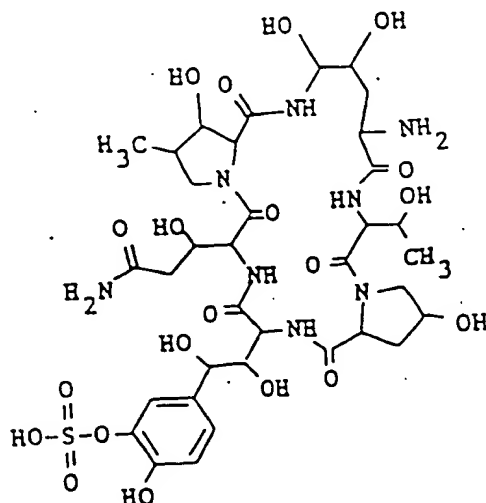
15 aryloxy(lower)alkanoyl which may have
one or more suitable substituent(s);

ar(lower)alkoxy(lower)alkanoyl which
may have one or more suitable
substituent(s);

20 arylamino(lower)alkanoyl which may
have one or more suitable
substituent(s); and

a pharmaceutically acceptable salt thereof,
which comprises

25 1) reacting a compound of the formula :

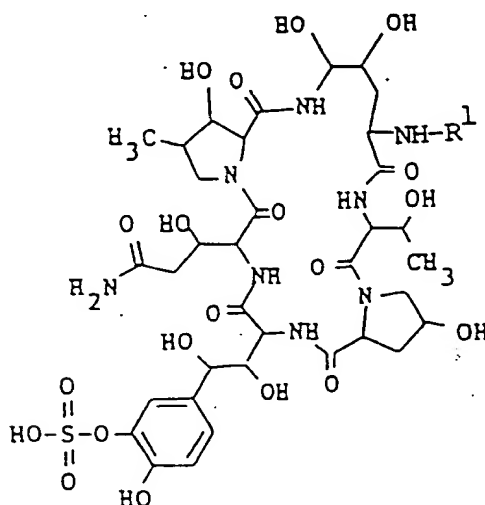


[II]

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :



wherein R^1 is defined above,
or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula:



wherein R^1 is defined above,
or a salt thereof.

14. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.
15. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.
16. A compound of claim 1 or a pharmaceutically

acceptable salt thereof for use as a medicament.

17. A method for the prophylactic and/or the therapeutic treatment of diseases caused by pathogenic microorganism which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

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